Congenital anomalies

Etiology, diagnosis and incidence

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2. Etiology, teratogens
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Congenital anomalies

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Definitions I

Congenital anomaly

Congenital Anomaly (CA) is an anomaly that affects a body part or physiologic function and is present at birth.

It is caused by the abnormal ontogenetic development of the fetus. The process is affected by genetic, environmental or both factors.

The disturbance of the regulation and development cascades take place on the level of tissue, cell or molecule.

Definitions II

Other „synonyms“

Congenital Malformation is a congenital anomaly of the structure of some body part.

Birth Defect or **Congenital Disorder** are nearly synonyms for the term Congenital Anomaly.

Chromosomal Aberrations are the numerical or structural abnormalities of the karyotype.

Genetic Disorders are the conditions caused by the mutation of the gene(s).

Definitions III

Nomenclature – type of anomaly

Malformation is caused by an abnormal development of the organ / tissue, that is abnormal from the beginning.

Disruption is caused by destructive process, that affects an organ / tissue, that started to develop normally.

Deformation is caused by an abnormal physical force, that damages healthy organ / tissue.

Dysplasia is caused by an abnormal organization of the cells in the organ / tissue.

Definitions IV

Nomenclature – association of anomalies

Isolated anomaly: an anomaly that is not associated with any other conditions (e.g. **isolated polydactyly**).

Sequence: multiple anomalies that result from the pathologic cascade caused by a primary insult (e.g. **Potter‘s sequence**).

Association: selected congenital anomalies that tend to develop all together – in an association (e.g. **VATER association**).

Syndrome: complex of phenotypic traits (anomalies) that are typical for defined clinical diagnosis (e.g. **Down syndrome**).

Definitions V

Teratogenesis

Teratogene is an agent that is able to affect normal ontogenetic development and lead to a congenital anomaly.

Mutagene is an agent that is able to affect the genetic information on the level of DNA or on the level of chromosomes.

Mutagens cause mutations.
Teratogens cause congenital anomalies.

Some mutagens are also teratogens. However, not all teratogens are mutagens.

Definitions VI

Classification

WHO - International Classification of Diseases (ICD).

International standard diagnostic classification for all general epidemiological, health management purposes and clinical use.

ICD-X Chapter XVII

Congenital malformations, deformations and chromosomal abnormalities

Q00 – Q99

Definitions VII

Classification - Groups

Q00-Q07 Congenital malformations of the nervous system
Q10-Q18 Congenital malformations of eye, ear, face and neck
Q20-Q28 Congenital malformations of the circulatory system
Q30-Q34 Congenital malformations of the respiratory system
Q35-Q37 Cleft lip and cleft palate
Q38-Q45 Other congenital malformations of the digestive system
Q50-Q56 Congenital malformations of genital organs
Q60-Q64 Congenital malformations of the urinary system
Q65-Q79 Congenital malf. and deform. of the musculoskeletal system
Q80-Q89 Other congenital malformations
Q90-Q99 Chromosomal abnormalities, not elsewhere classified

The whole classification can be found on the WHO website:
http://www.who.int/classifications/apps/icd/icd10online/

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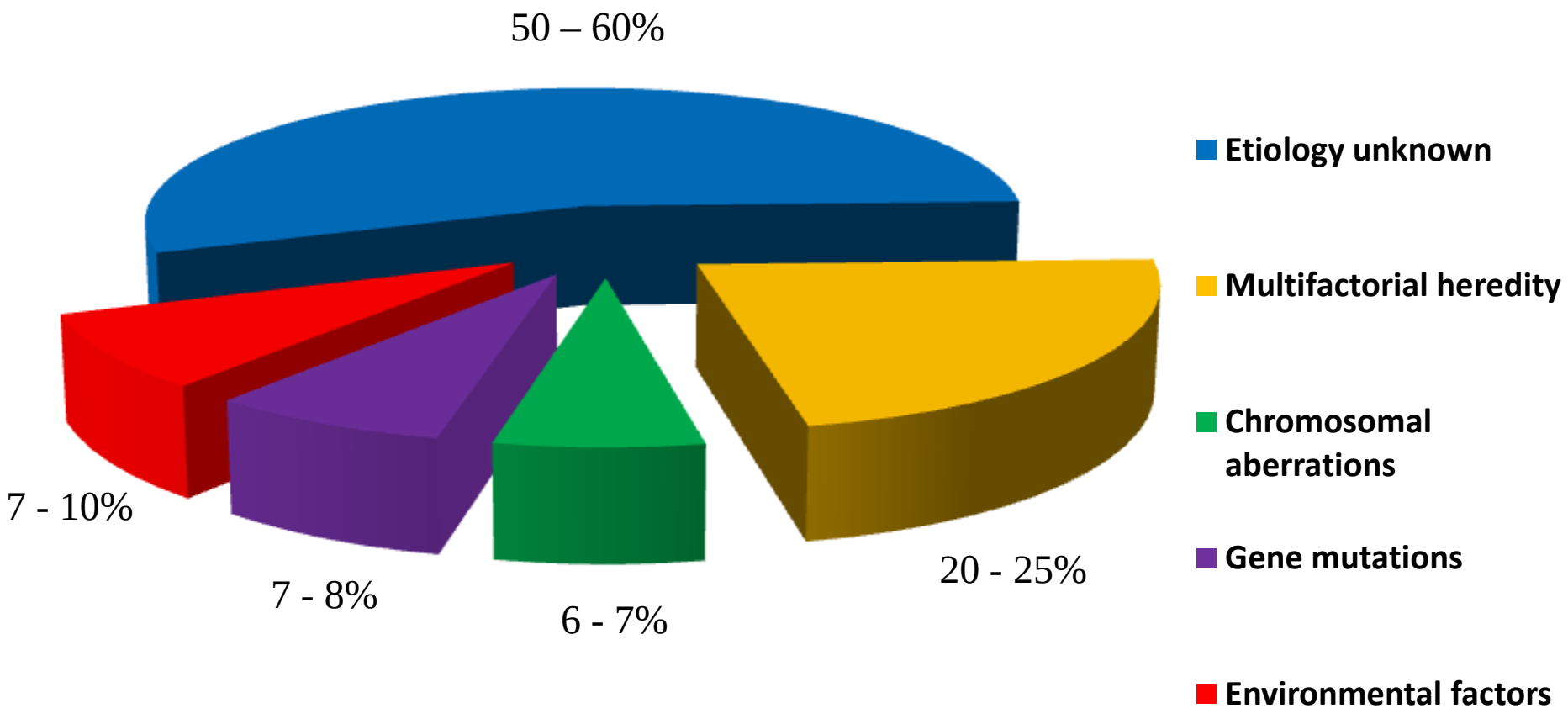
Etiology I

What causes congenital anomalies?

- Genetic factors
- Environmental factors
- Unknown factors

Etiology II

Etiology of the congenital anomalies in man



From: Moore K. L., Persaud T. V. N.; The Developing Human: Clinically Oriented Embryology, 6th Edition; 1998

Genetics I

The role of genetics in the etiology of CM‘s

- Monogenic inheritance
- Polygenic / Multifactorial inheritance
- Chromosomal aberrations
- Other (epigenetics etc.)

Genetics II

Monogenic inheritance

Some congenital malformation are inherited as a monogenic trait. There are several genes, whose mutations are associated with selected congenital anomalies. The reference can be found in Mendelian Inheritance in Man (MIM). Prenatal diagnosis and management of the genetic counseling is less difficult.

- **Marfan syndrome (Q87.4; MIM: 154700)**
- **Ehlers – Dahnlos syndrome (Q79.6; MIM: 13000)**
- **Osteogenesis imperfecta (Q78.0; MIM: 166200)**
- **Achondroplasia (Q77.4; MIM: 100800)**
- **Holoprosencephaly (Q04.2; MIM: 236100)**
- **Xeroderma pigmentosum (Q82.1; MIM: 278830)**

Genetics III

Multifactorial (and polygenic) inheritance

Polygenic inheritance means, that more than one gene affect the selected phenotypic trait (disease, anomaly…)

Multifactorial inheritance means, that not only genetic factors (genes), but also the environmental factors affect the selected trait.

In practice – it is not always easy to distinguish between polygenic and multifactorial – we usually use the term **multifactorial**.

Today, the etiology of the majority of congenital anomalies is believed to be multifactorial.

Genetics IV

Chromosomal aberrations

Numerical aberrations – abnormalities in total number of the chromosomes. (e.g. trisomy, monosomy)

Structural aberrations – abnormalities in the structure of the chromosomes. (e.g. deletion, duplication, inversion, translocation)

Autosomal aberrations – abnormalities of the autosomes.

Gonosomal aberrations – abnormalities of the gonosomes.

Genetics V

Chromosomal aberrations - Syndromes

- **Down Syndrome** (47,XX,+21) or (47,XY,+21)
- **Edwards Syndrome** (47,XX,+18) or (47,XY,+18)
- **Patau Syndrome** (47,XX,+13) or (47,XY,+13)
- **Klinefelter Syndrome** (47,XXY)
- **Turner Syndrome** (45,X)
- **Triple X Syndrome** (47,XXX)
- **XYY Syndrome** (47,XYY)
- **Cri du Chat Syndrome** (46,XX,del(5p)) or (46,XY,del(5p))
- **Wolf-Hirschhorn Syndrome** (46,XX,del(4p)) or (46,XY,del(4p))
- **Di-George Syndrome** (46,XX,del(22q11.2)) or (46,XY,del(22q11.2))

….. And many others…..

Note: other variants of the karyotype for those syndromes are possible

Genetics VI

Epigenetics – The role of genomic imprinting

Prader – Willi Syndrome X Angelman Syndrome

Caused by deletion or inactivation 15q11-q13 of PATERNAL origin

Can be also caused by UNIPARENTAL DISOMY (maternal chrom. 15 only)

ICD-10: Q87.1 MIM: 176270

- **mild to moderate mental retardation**
- **hyperphagia + obesity**
- **small hands and feet**
- **hypogonadism**
- **decreased mean height in adulthood**

Caused by deletion or inactivation 15q11-q13 of MATERNAL origin

Can be also caused by UNIPARENTAL DISOMY (paternal chrom. 15 only)

ICD-10: Q93.5 MIM: 105830

- **severe mental retardation**
- **paroxysm of inappropriate laughter**
- **EEG abnormalities**
- **ataxia + jerky arm movements**
- **„Happy Puppet Syndrome“**

Teratogens I

Environmental factors

There are many environmental factors that cause congenital anomalies, or are able to cause them in specific situations.

Those factors are commonly known as **teratogens**.
However - the effect of teratogens is dependent on the genetics. The genotype can modify the teratogenic effect.

There are three main groups of teratogens:

1. **Physical**
2. **Chemical**
3. **Biological**

Teratogens II

Physical teratogens

- **X-rays** (common diagnostic doses are not dangerous)
- **Ionizing radiation** (e.g. gamma radiation)
- **High temperature** (sauna, fever)
- **Mechanical factors** (amniotic bands, oligohydramnion)

Ultrasonography and electromagnetic field seem to be safe.

Teratogens III

Chemical teratogens

- chemical substances used in industry or agriculture (organic solvents, paints, polychlorinated biphenyls, heavy metals)
- **alcohol** (cause Fetal alcohol syndrome)
- products of cigarette **smoking** (teratogenic effect of marihuana smoking was also proved)
- other drugs (e.g. cocaine), doping (steroids)
- **cytostatics** and some other groups of **medicaments** (antiepileptics, antibiotics, warfarine, ACE-inhibitors)

Teratogens IV

Drugs and teratogenic effect

The intensive study of teratogenic effect of the drugs started after the „**thalidomide affair**“ in the sixties of 20th century.

The current boom of pharmaceutical industry provides many new medicaments each year. The safety of those substances must be tested.

Teratogenic effect is **species-dependent**. It is possible, that human embryo will not be affected by the same substance, that affects rat embryos.

The same dose of substance could be teratogenic in human, but needn‘t to be teratogenic at all in rats or other animals. The effect is **dose-dependent**.

The same substance can be teratogenic only in a specific week of pregnancy. It can only affect the development of a specific organ / tissue. The effect is **time-dependent**.

It is **not easy to prove**, that the congenital malformation was caused by the usage of a specific drug during pregnancy. Usually, there is not enough data. It is necessary to collect all data possible about such risk – pregnancies.

Teratogens V

Drugs and teratogenic effect

During the time of **blastogenesis**, the damage caused by the teratogens cause **no anomalies**. The embryo is either able to repair all damage taken, or it stops to develop and dies.
The time of **organogenesis** (3th-12th week of pregnancy) is the **critical period** for most teratogens. The morphologic anomalies are usually caused during this period.
The **second and third trimester** is not so critical, however the toxic effect of some substances is pathologic as well.

The teratogenic effect of the drugs: 1) proved 2) presumable 3) possible 4) couldn‘t be excluded

Teratogens VI

Drugs - Teratogenic effect proved

Alcohol (facial dysmorphy, brain growth retardation, congenital anomalies of the heart)

Warfarine (chondrodysplasia punctata, risk of abortion)

Retinoids (anomalies like Di-George syndrome, anomalies of CNS, anomalies of the internal ear)

Aminopterine + Methotrexate (anomalies of cranium and skeleton, anencephaly)

Thalidomide (abnormal development of long bones, phocomelia, polydactyly, syndactyly, oligodactyly and other malformations)

Teratogens VII

Drugs - Teratogenic effect presumable

Fenytoine (congenital anomalies of the heart, failure of th CNS closure, cleft palate)

Trimetadione (anomalies of the heart, anomalies of the urogenital system, mental retardation)

Valproate (facial dysmorphy, defects of CNS)

Lithium (anomalies of the heart, Ebstain‘s anomaly)

Teratogens VIII

Drugs - Teratogenic effect possible

Amfetamine (congenital anomalies of the heart, exencephaly, atresia of bile ducts)

Diazepame (cleft lip and cleft palate)

ACE-Inhibitors (hypoplasia of the skull, renal dysgenesis)

Corticosteroids (cleft palate, renal atrophy)

Androgens (masculinization of the external genitalia)

Progesteron (virilization, anomalies of the hearth, anomalies of the CNS, defects of the extremities, esophageal atresia)

Teratogens IX

Biological teratogens

- **Infectious agents**
  TORCH (acronym for most important teratologic agents)
    - **T**oxoplasma
    - **O**ther viruses
    - **R**ubivirus
    - **C**ytomegalovirus
    - **H**erpesvirus

- **Diseases of the mother**
    - **Diabetes mellitus (DM)**
    - **Phenylketonuria (PKU)**

Teratogens X

Selected infectious agents

Rubivirus (cataract, deafness, anomalies of the heart, microcephaly, mental retardation)
Cytomegalovirus (microcephaly, chorioretinitis, deafness, hepatosplenomegaly)
Varicella-Zoster virus (microcephaly, chorioretinitis, defects of the extremities, mental retardation, cataract)
Parvovirus B-19 (hydrops fetalis, anemy, malformation of the heart)
Influenzavirus (failure of the CNS closure)
Coxsackie virus (fetal pancreatitis and fetal meningoencephalitis)
HIV (immunodeficiency, dysmorphy)
Treponema pallidum (failure of teeth development, IUGR, hydrops fetalis)
Toxoplasma gondii (hydrocephaly, microcephaly, chorioretinitis, blindness)

Teratogens XI

Sources of information about drugs

State Institute of Drug Control of Czech Republic
http://www.sukl.cz/

European Medicines Agency
http://www.emea.europa.eu/

U S Food and Drug Administration
http://www.fda.gov/

Teratogens XII

Teratology Information Services / Societies

Czech Teratology Information Service (CZTIS)
http://old.lf3.cuni.cz/histologie/english/33.htm

European Network Teratology Information Services
http://www.entis-org.com/

Organization of Teratology Information Specialists
http://www.otispregnancy.org/

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Congenital Anomalies I

The groups selected for this lecture

- Neural tube defects (NTD)
- Abdominal wall defects (AWD)
- Congenital anomalies of the kidneys
- Chromosomal aberrations

In descriptions we use the official definitions provided by ICBDSR organization - http://www.icbdsr.org/

Congenital Anomalies II

Neural tube defects

Defect in closure of the neural groove. Normal neural tube is not formed.

Anencephaly represents a defect in closure at the anterior part of the neural groove.

Defects at the mid- or caudal neural groove cause meningo(myelo)cele or spina bifida.

Congenital Anomalies III

Anencephaly

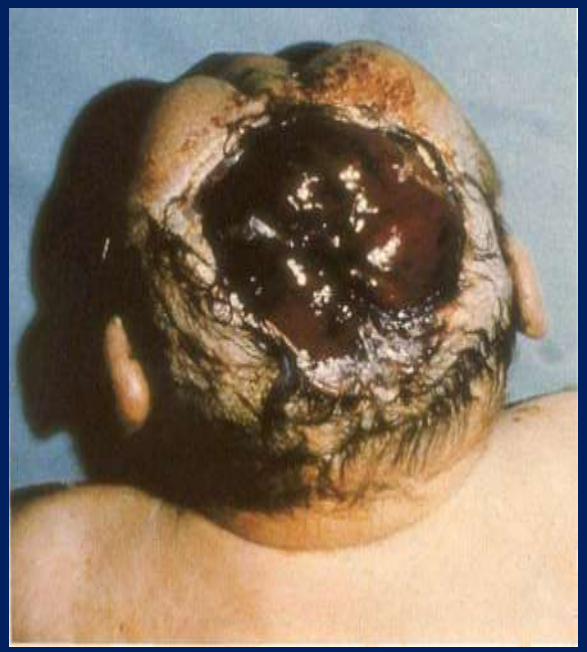
Anencephaly is a congenital anomaly characterized by **the total or partial absence of the cranial vault , the covering skin, and the brain missing or reduced to small mass(e)**.

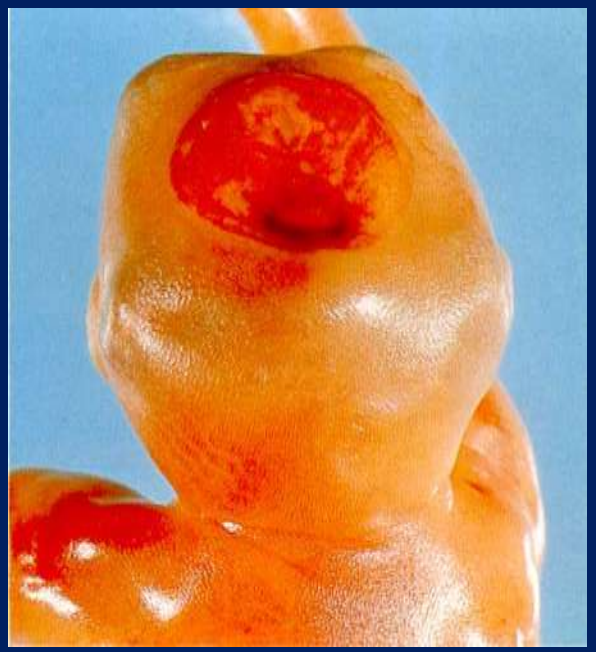
Include craniorachischisis. Include infants with iniencephaly and other neural tube defects as encephalocele or open spina bifida, when associated with anencephaly.

Exclude acephaly, that is, absence of head observed in amorphous acardiac twins.

Congenital Anomalies IV

Anencephaly





Partial absence of the cranial vault

Brain reduced to small mass

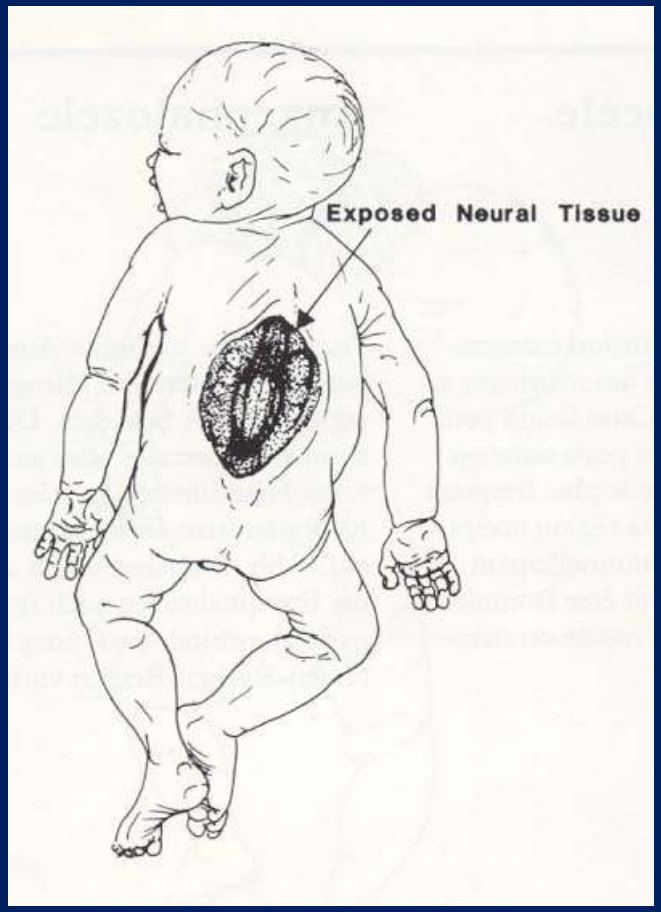
Congenital Anomalies V

Spina Bifida

Spina bifida is a family of congenital anomalies defects in the closure of the spinal column characterized by **herniation or exposure of the spinal cord and/or meninges through an incompletely closed spine.** Include meningocele, meningomyelocele, myelocele, myelomeningocele, rachischisis. Spina bifida is not counted when present with anencephaly.
Exclude: spina bifida occulta, sacrococcygeal teratoma without dysraphism.

Congenital Anomalies VI

Spina Bifida



Defects in the closure of the spinal column

Exposure of the spinal cord

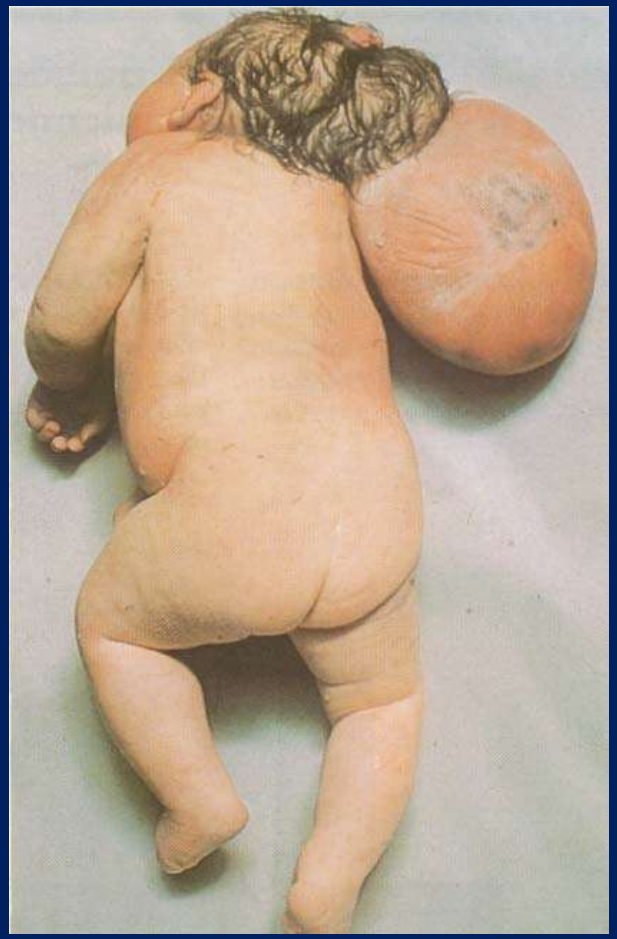
Congenital Anomalies VII

Encephalocele

Encephalocele is a congenital anomaly characterized by **herniation of the brain and/or meninges through a defect in the skull**. Encephalocele is not counted when present with spina bifida.

Congenital Anomalies VIII

Encephalocele



Herniation of the brain and/or meninges through a defect in the skull.

Congenital Anomalies IX

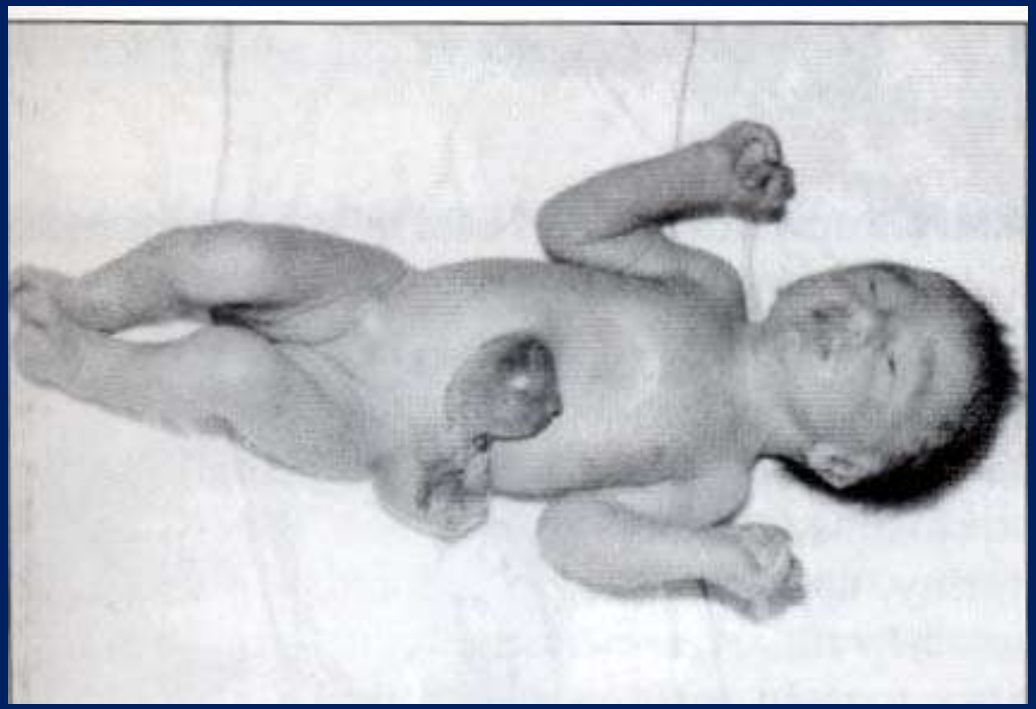
Omphalocele

Omphalocele is a congenital anomaly characterized by **herniation of abdominal contents through the umbilical insertion** and covered by a membrane which may or may not be intact.

Exclude gastroschisis (para-umbilical hernia), aplasia or hypoplasia of abdominal muscles, skin-covered umbilical hernia.

Congenital Anomalies X

Omphalocele



Herniation of abdominal contents through the umbilical insertion

Congenital Anomalies XI

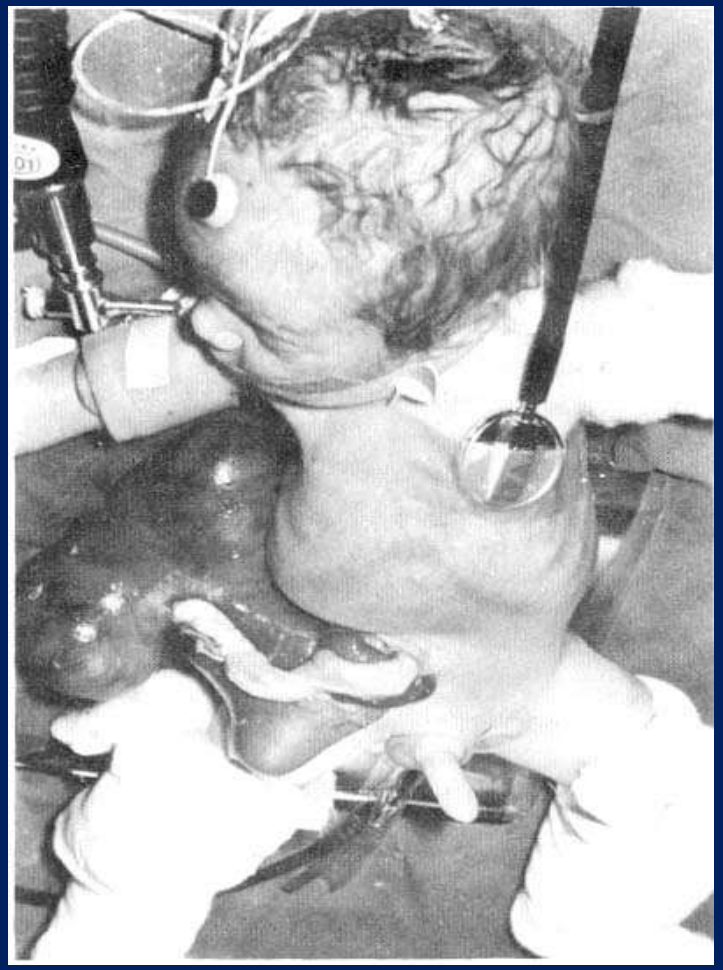
Gastroschisis

Gastroschisis is a congenital anomaly characterized by **visceral herniation through an abdominal wall defect lateral to an intact umbilical cord** and not covered by a membrane.

Exclude a- or hypoplasia of abdominal muscles, skin-covered umbilical hernia, omphalocele.

Congenital Anomalies XII

Gastroschisis



Herniation of abdominal contents through an abdominal wall defect lateral to an intact umbilical cord

Congenital Anomalies XIII

Diaphragmatic hernia

Diaphragmatic hernia is a congenital anomaly characterized by **herniation into thorax of abdominal contents through a defect of the diaphragm.** Include total absence of the diaphragm.

Exclude hiatus hernia, eventration and phrenic palsy.

Congenital Anomalies XIV

Hydrocephaly

Hydrocephaly is a congenital anomaly characterized by **dilatation of the cerebral ventricles, not associated with a primary brain atrophy, with or without enlargement of the head**, and diagnosed at birth.
Not counted when present with encephalocele or spina bifida.
Exclude: macrocephaly without dilatation of ventricular system, skull of macerated fetus, hydranencephaly, holoprosencephaly, and postnatally acquired hydrocephalus.

Congenital Anomalies XV

Congenital anomalies of the kidneys

Renal agenesis is a congenital anomaly characterized by **complete absence of kidneys bilaterally or severely dysplastic kidneys**.

Cystic kidney is a congenital anomaly characterized by **multiple cysts in the kidney**.
Include infantile polycystic kidney, multicystic kidney, other forms of cystic kidney and unspecified cystic kidney.
Exclude single kidney cyst.

Congenital Anomalies XVI

Polycystic kidney disease - Genetics

Autosomal dominant form (MIM: 173900)

- **PKD1** gene mutation (16p13.3-p13.12, MIM: 601313)
- **PKD2** gene mutation (4q21-q23, MIM: 173910)
- **PKD3** gene mutation ?? (not yet localized, MIM: 600666)

Autosomal recessive form (MIM: 263200)

- **PKHD1** gene mutation (6p21.1-p12, MIM: 606702)

Congenital Anomalies XVII

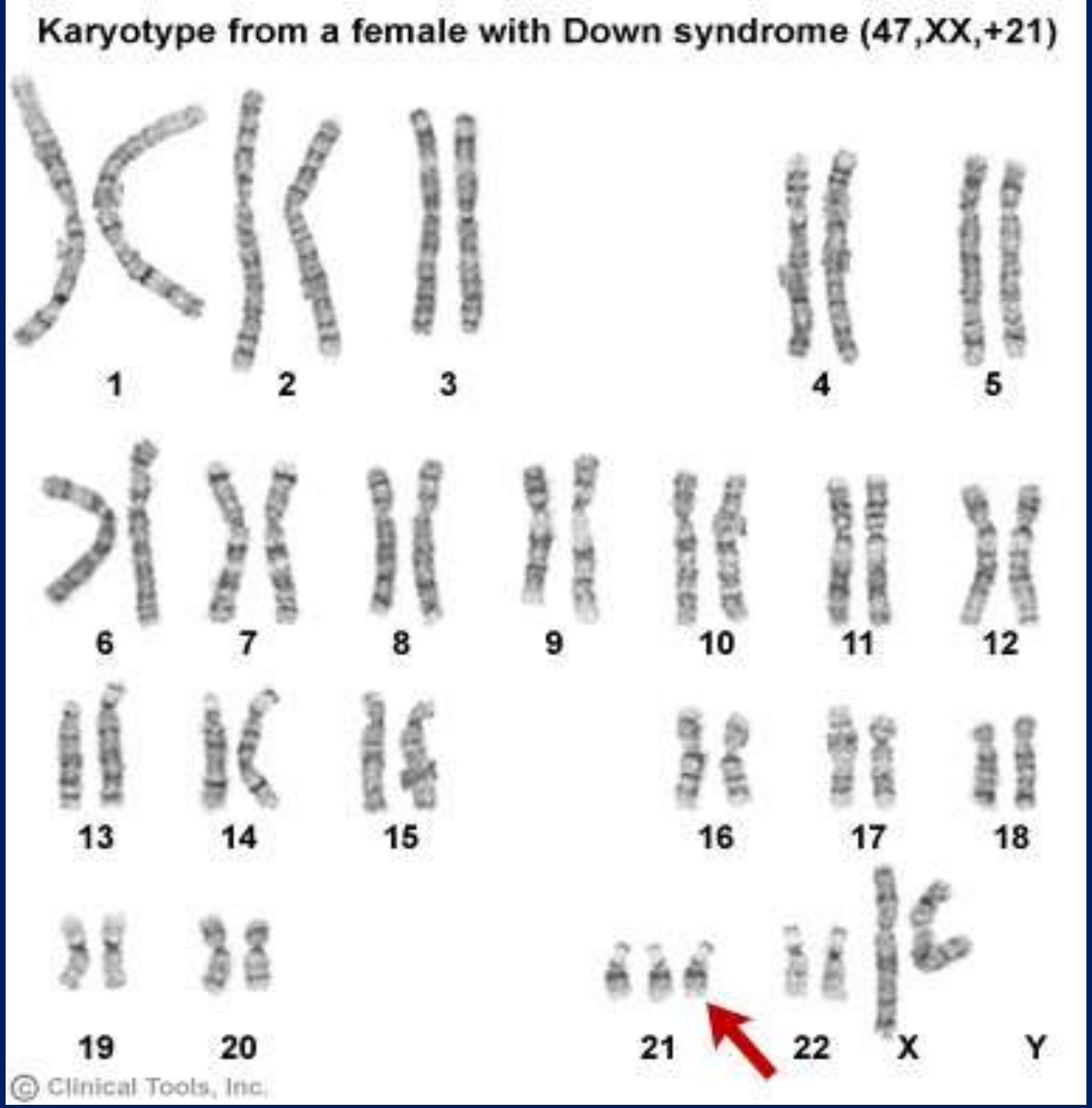
Down syndrome

Down syndrome is a congenital **chromosomal** anomaly syndrome characterized by a well known pattern of minor and major anomalies and associated with excess chromosomal 21 material.
Include trisomy mosaicism and translocations of chromosome 21.

Common karyotype – trisomy 21
47,XX,+21 (female) or 47,XY,+21 (male)

Down Syndrome I

Typical face
Upslanting palpebral fissures
Mental retardation
Hypotonia
Macroglossia
Simian crease on hand
Eye / Sight anomalies
Anomalies of the heart



From: http://images1.clinicaltools.com/

Congenital Anomalies XVIII

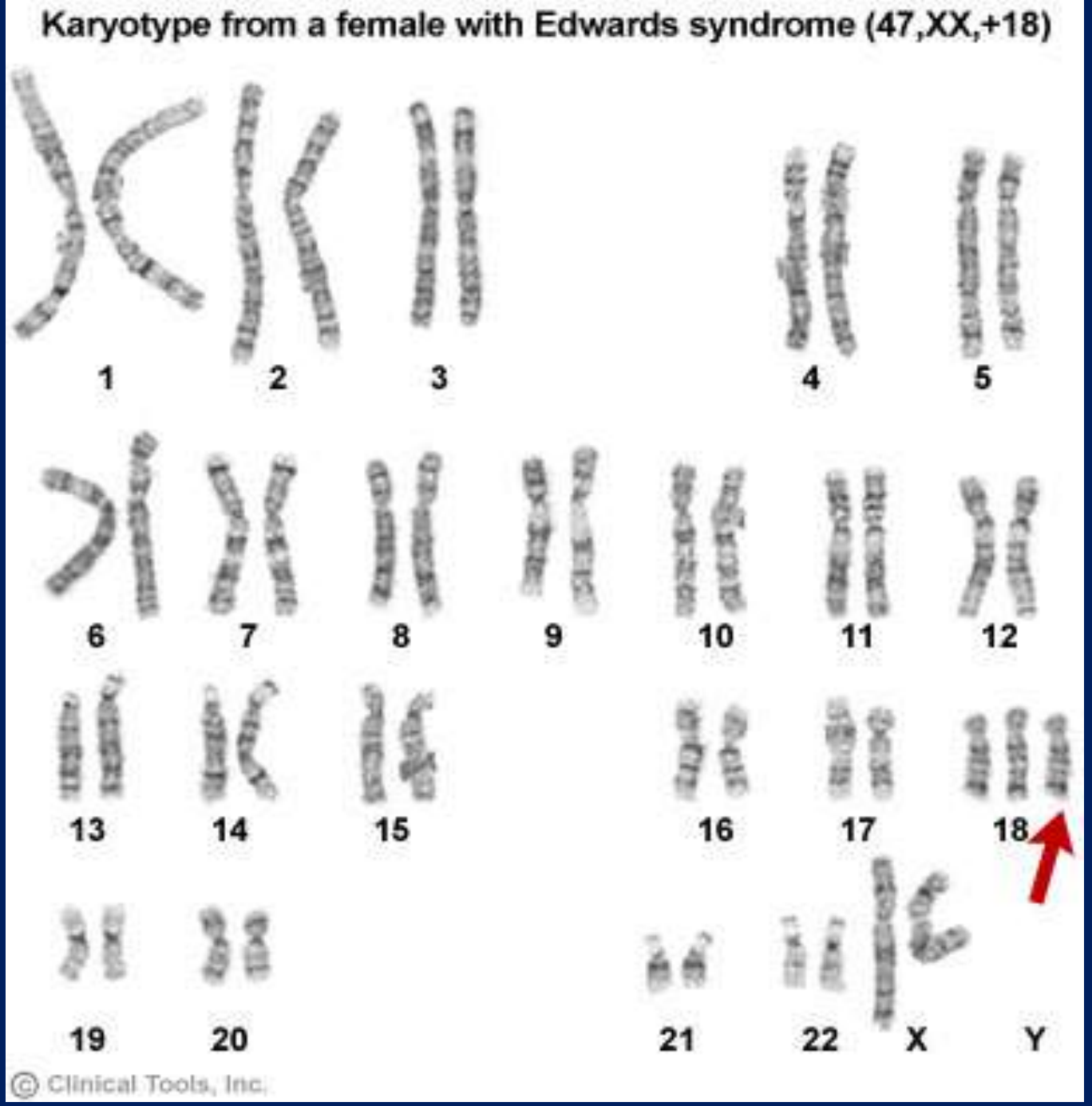
Edwards syndrome

Edwards syndrome is a congenital **chromosomal** anomaly syndrome characterized by a well known pattern of minor and major anomalies and associated with extra chromosome 18 material.
Include translocation and mosaic trisomy 18.

Common karyotype – trisomy 18
47,XX,+18 (female) or 47,XY,+18 (male)

Edwards Syndrome I

Hypertonicity
Prominent occiput
Mental retardation
Low-set auricles
Clenched hands with overlapping fingers



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Congenital Anomalies XIX

Patau syndrome

Patau syndrome is a congenital **chromosomal** anomaly syndrome characterized by a well known pattern of minor and major anomalies and associated with extra chromosome 13 material.
Include translocation and mosaic trisomy 13.

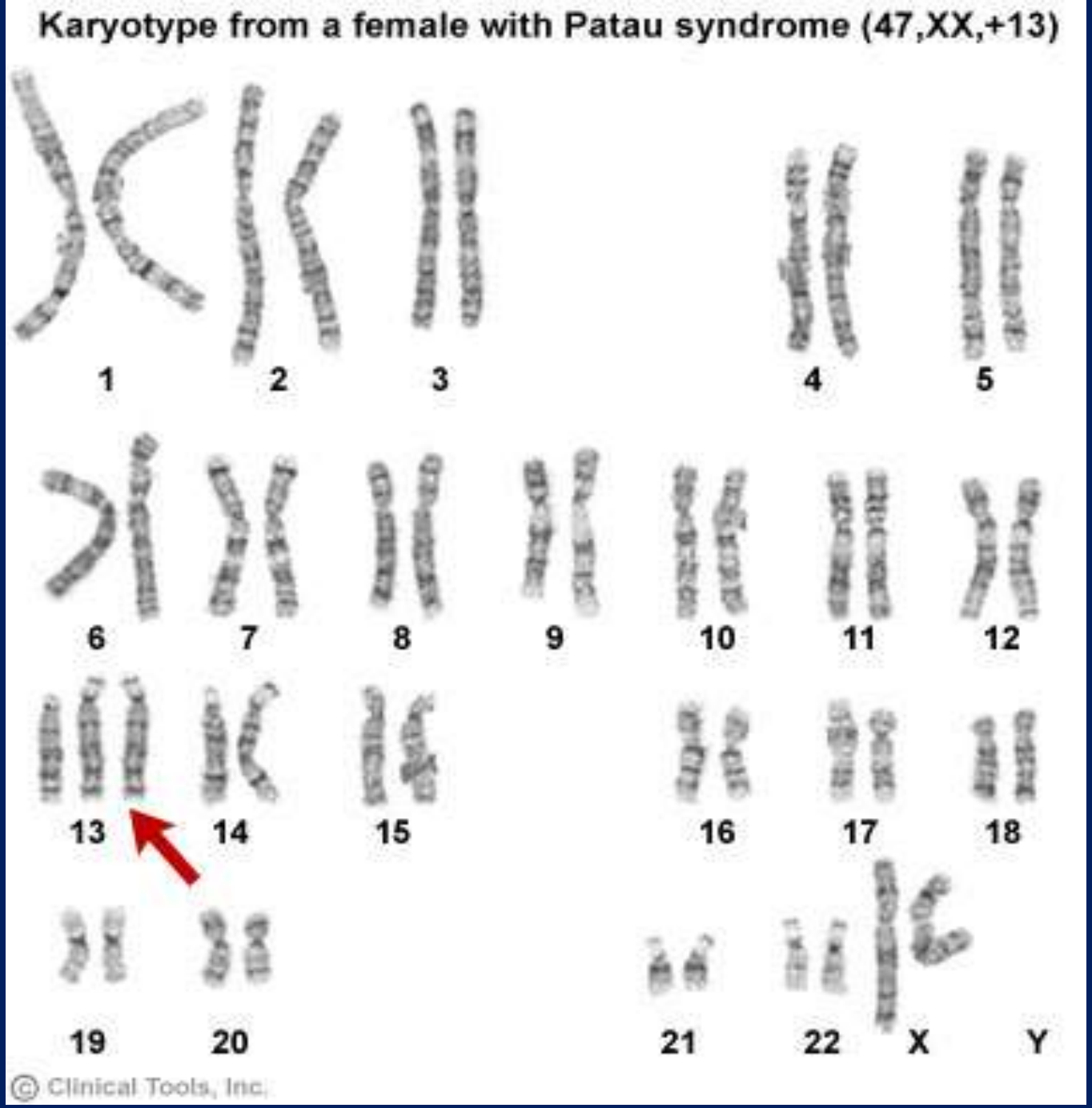
Common karyotype – trisomy 13
47,XX,+13 (female) or 47,XY,+13 (male)

Patau Syndrome I

Variable defects in facial development
Cleft lip, cleft palate or both
Microcephaly with sloping forehead
Variable abnormalities of the eye
Severe anomalies of the CNS
Capillary hemangiomata
Polydactyly
Malformations of the heart
Skin abnormalities
Abnormalities of the genitalia

Patau Syndrome II

Variable defects in facial development
Cleft lip, cleft palate or both
Microcephaly with sloping forehead
Variable abnormalities of the eye
Severe anomalies of the CNS
Capillary hemangiomata
Polydactyly
Malformations of the heart
Skin abnormalities
Abnormalities of the genitalia



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Congenital Anomalies XX

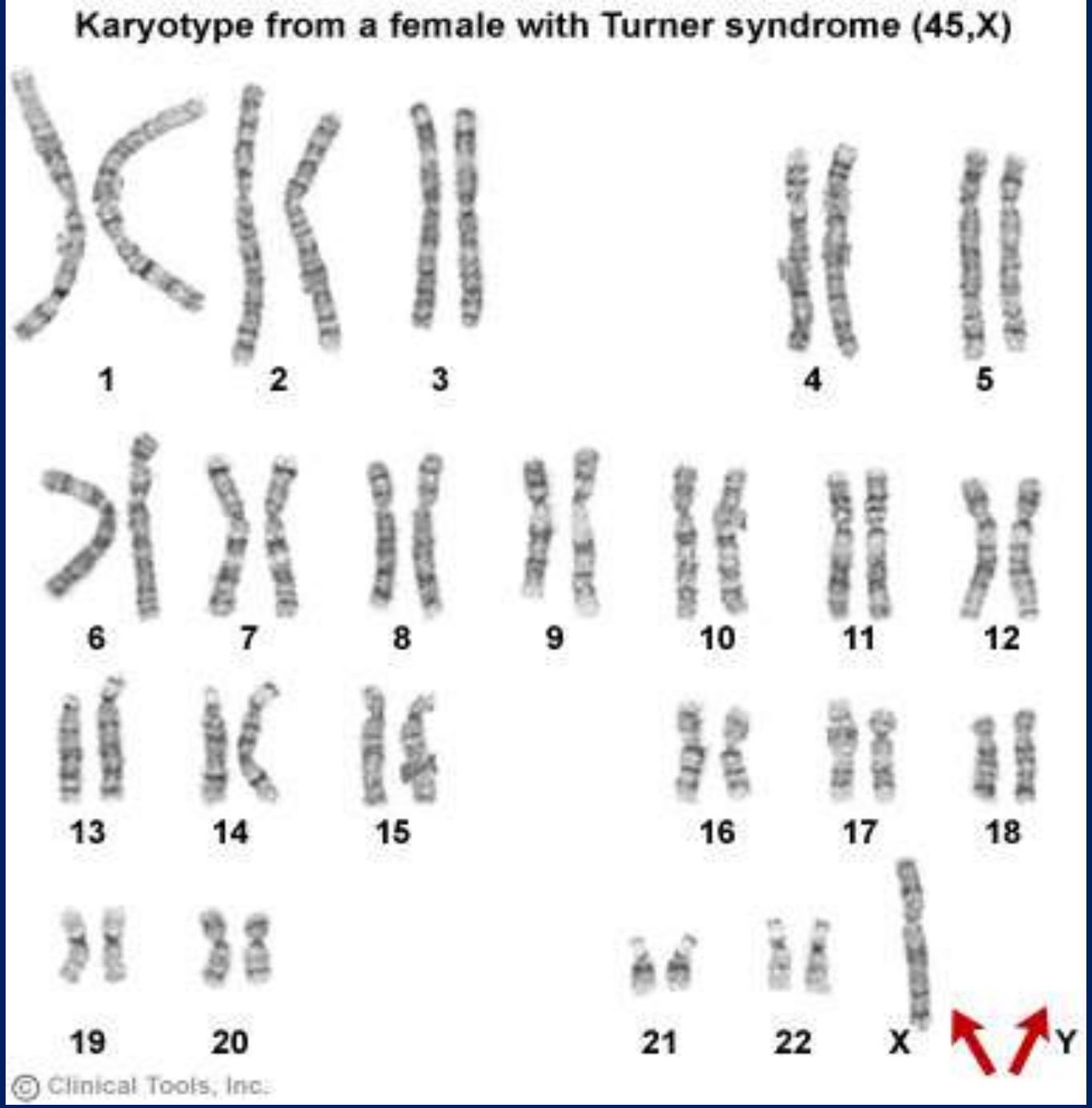
Turner syndrome

Turner syndrome is a congenital **chromosomal** anomaly syndrome characterized by a well known pattern of minor and major anomalies and associated with missing material of the second gonosome.
Include translocations, structural abnormalities of the X chromosome and mosaic monosomy X.

Common karyotype – monosomy X
45,X (female)
According to ISCN 2005 norm the entry – 45,X0 is **no longer valid**!
Note: monosomy Y is lethal

Turner Syndrome

Ovarian hypoplasia / dysgenesis; infertility
Small statue (mean final height 143cm)
Loose nuchal skin
Congenital lymphedema
Cardiac anomalies (coarctation of aorta)



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Congenital Anomalies XXI

Useful links

OMIM – Online Mendelian Inheritance in Man
http://www.ncbi.nlm.nih.gov/sites/entrez?db=omim

eMedicine - The original open access comprehensive medical textbook
http://www.emedicine.com/

Orphanet - The portal for rare diseases and orphan drugs
http://www.orpha.net/

Congenital anomalies

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Prenatal diagnosis I

Primary prevention

The main goal is to prevent anomaly or malformation before they develop (that means before conception or during pregnancy).
The women should avoid the pregnancy in very low or very high age. The pregnancy should be planned.
The parents should avoid any contact with mutagens or teratogens.
No stress, smoking, drugs and alcohol during pregnancy.
Clinical geneticist should be consulted in advance – if necessary (repeated abortions, congenital anomalies in family, genetic diseases).
Good compensation of mother‘s diseases (DM, PKU etc.)
Supplementation with folic acid

Prenatal diagnosis II

Secondary prevention

The main goal is to **prevent the birth** of a child with a congenital anomaly. However, the termination itself is not a prevention.
We can **terminate the pregnancy** in order to prevent such a birth. However, the termination **may not be legal** in each country.
In the Czech Republic it is legal to terminate the pregnancy because of severe genetic reasons till **24th week** of pregnancy.
Prenatal diagnosis is therefore very important, because we need the best information available about the condition of the fetus. If a severe condition is diagnosed, we may offer termination of pregnancy, prenatal therapy or special treatment in perinatologic period.

Prenatal diagnosis III

Methods

There are two main groups of methods in prenatal diagnosis:

Invasive methods

Amniocentesis (AMC), Chorionic villus sampling (CVS), Cordocentesis (CC), Fetoscopy, Fetal biopsy

Noninvasive methods

Biochemical screening (requires mother‘s blood sample), Ultrasound, Magnetic resonance

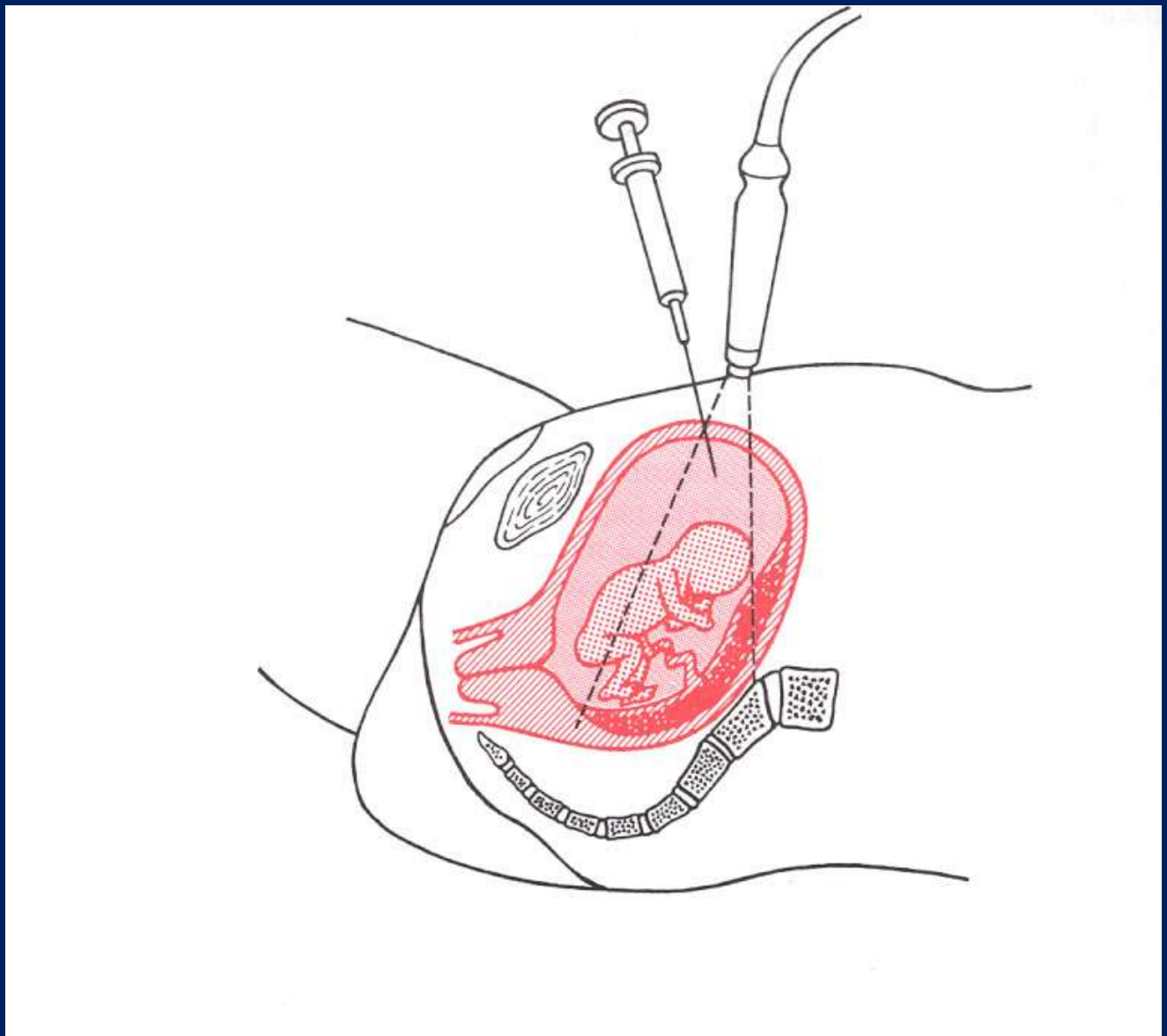
Prenatal diagnosis IV

Amniocentesis

Amniocentesis is commonly used invasive method, that is able to obtain a sample of the amniotic fluid, including amniocytes. Those cells can be cultivated for cytogenetic analysis. Using QF-PCR we can have preliminary results (for most common trisomies) in 2 days (rather than in 2 weeks – we need for cultivation and karyotype).

Early amniocentesis can be made earlier then the standard amniocentesis (14th week – rather than 16th week). However, we cannot obtain so much amniotic fluid.

Amniocentesis



Prenatal diagnosis V

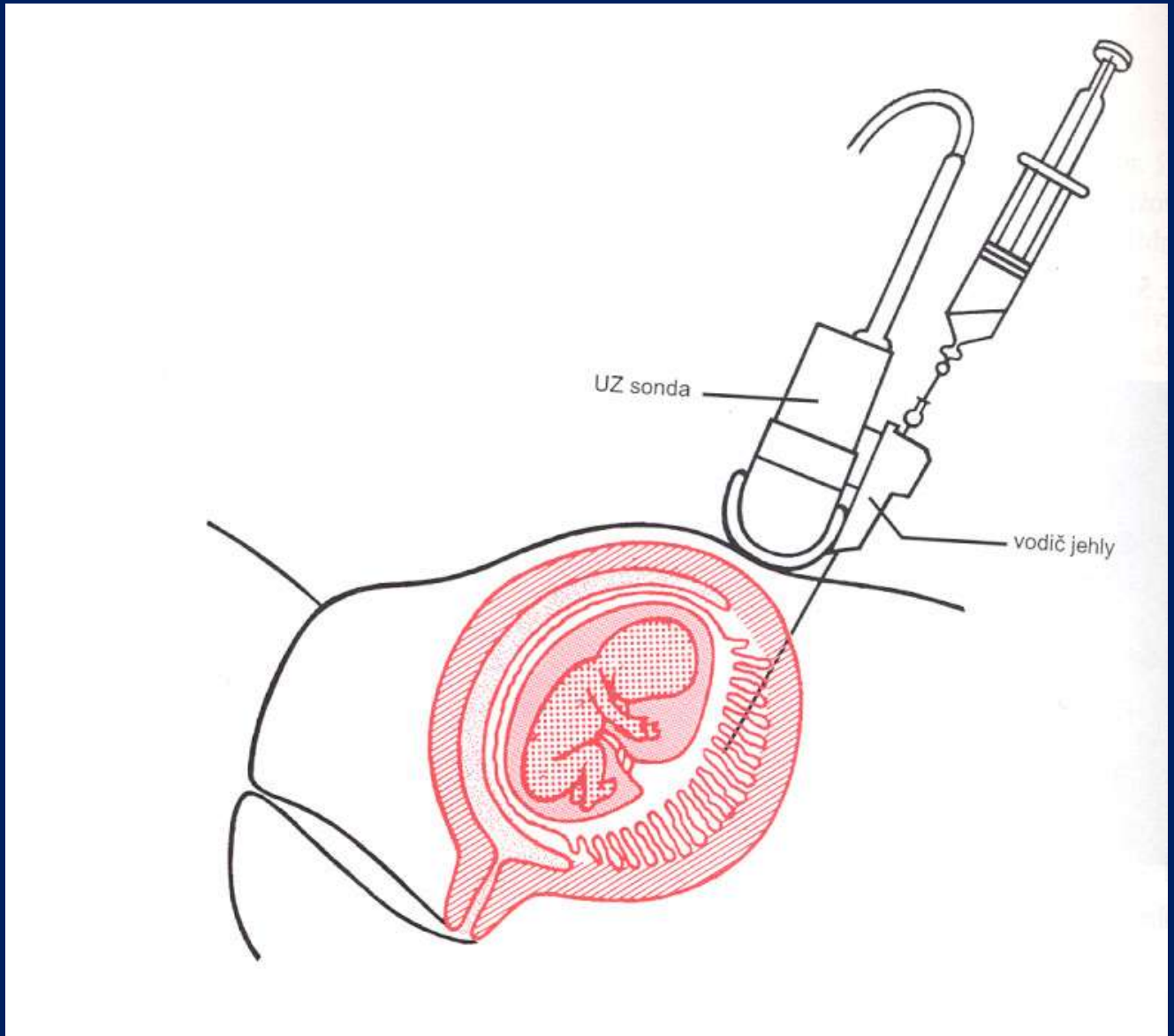
Other Invasive methods

CVS can be made very soon, after the 11th week of gestation. This allows early diagnosis. However, there is a risk of confined placental mosaicism (CPM), what can make the decision more difficult.

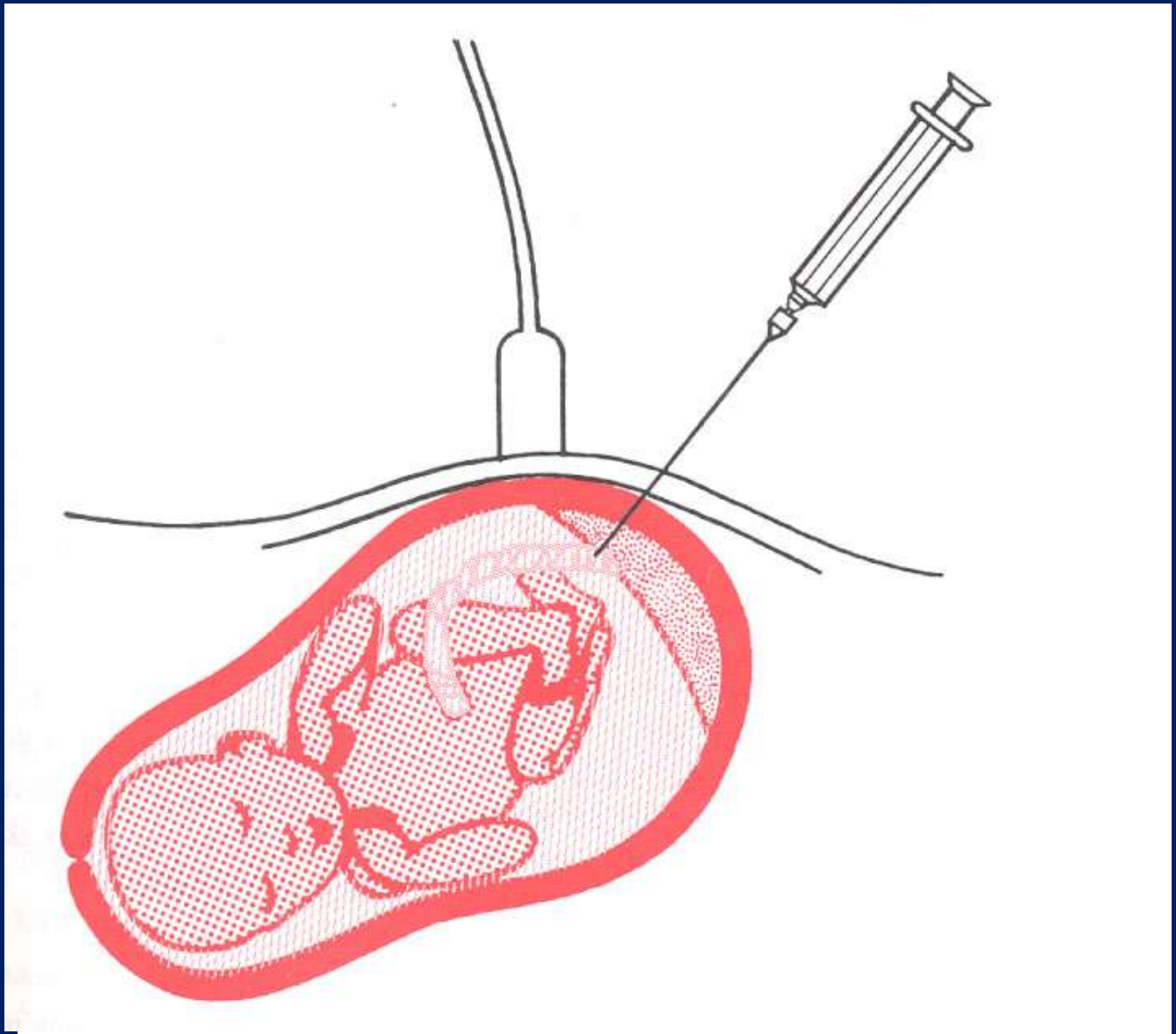
Cordocentesis is usually made after the 20th week. The sample of blood allows us to make hematologic tests, as well as the cultivation.

Fetoscopy and **fetal biopsy** are very rare today. Fetoscopy can be used in order to confirm some dermatologic anomalies (Ichtyosis vulgaris). Biopsy can obtain a sample of fetal skin (or other tissue) for histopathological analysis.

CVS



Cordocentesis



Prenatal diagnosis VI

Biochemical screenings

Combined screening of the first trimester

This test combines the ultrasound diagnostics (**NT** – Nuchal Translucency measurement, **NB** – nasal bone presence / absence, tricuspidal regurgitation) with biochemical test of maternal serum (using **PAPP-A** and **free beta-HCG** subunit).
Some other biochemical markers can be examined in 1st trimester.

Biochemical screening of the second trimester

The blood sample from the mother is obtained usually after 16th week. **uE3** (unconjugated estriol), **HCG** (human chorionic gonadotropine) and **AFP** (alfa-fetoprotein) are analyzed.

Prenatal diagnosis VII

Imaging methods

Ultrasound diagnostics

Ultrasound diagnosis is commonly used and provide detailed morphological information. Therefore - the majority of structural anomalies is diagnosed thanks to USG diagnostics. Special methods – like **fetal echocardiography** – may provide additional information.

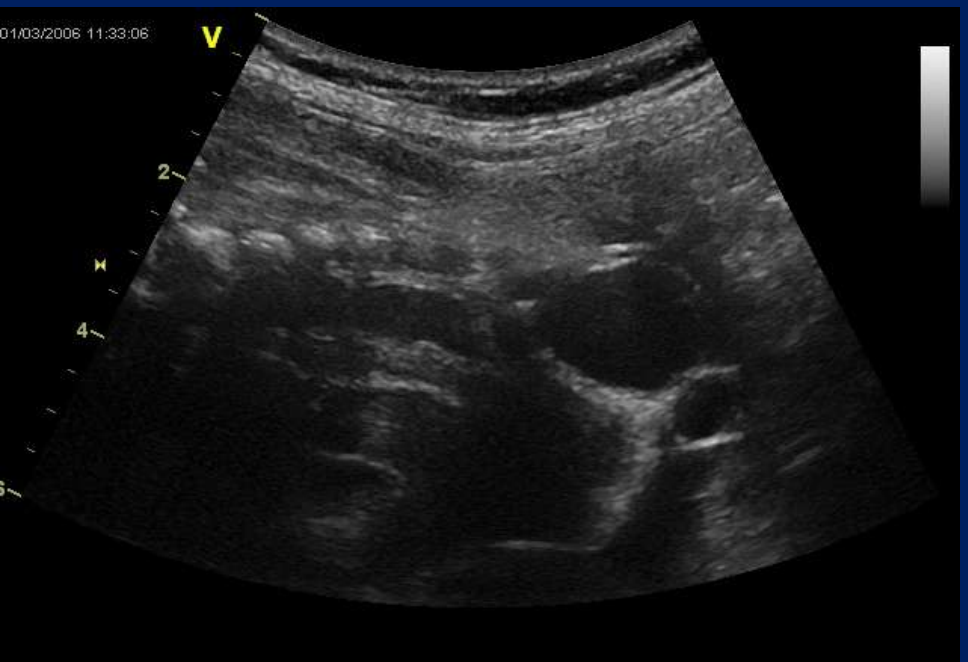
Magnetic resonance imaging

MRI is relatively new method in prenatal diagnosis and is still quite rare. The image processing must be very quick, because the fetus is moving. However - this method is excellent in detection of brain and other soft-tissue anomalies.

USG images I

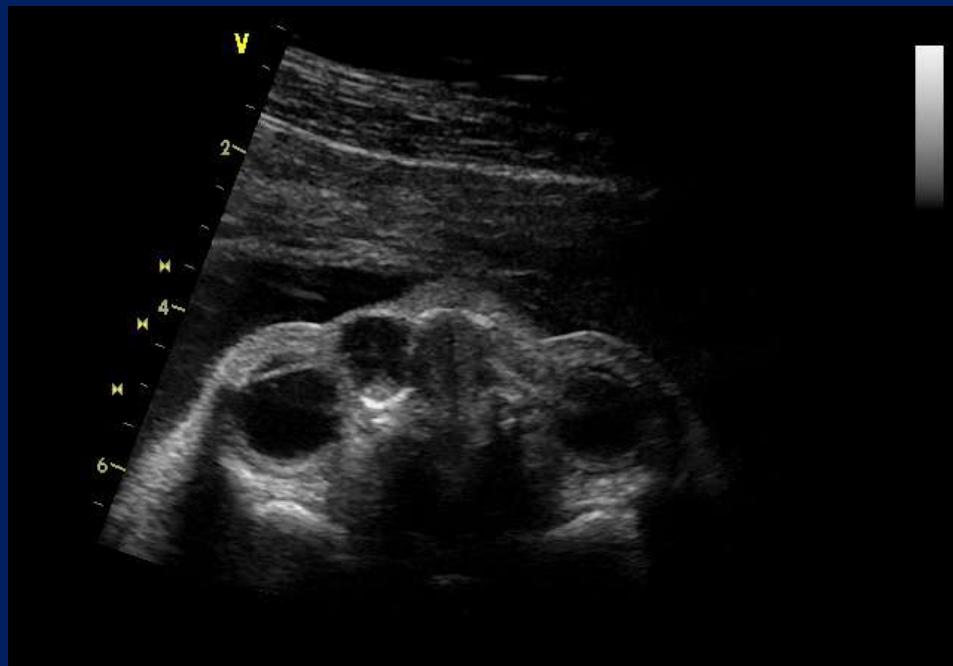
Sacral Dermoid

Provided by Miroslav Břešťák, MD,
PRONATAL sanatorium



Facial Tumor

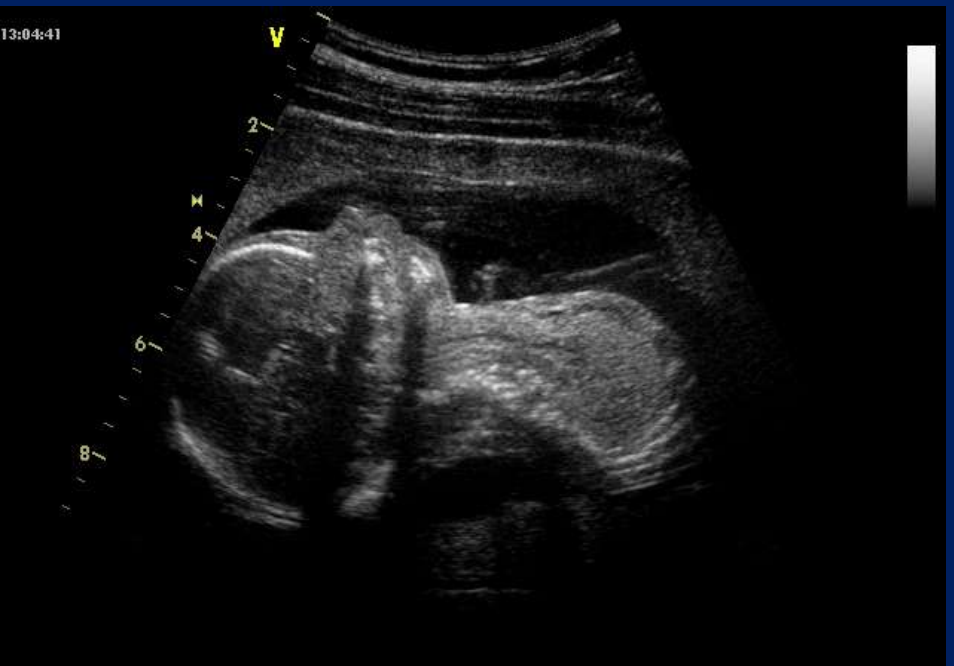
Provided by Miroslav Břešťák, MD,
PRONATAL sanatorium



USG images II

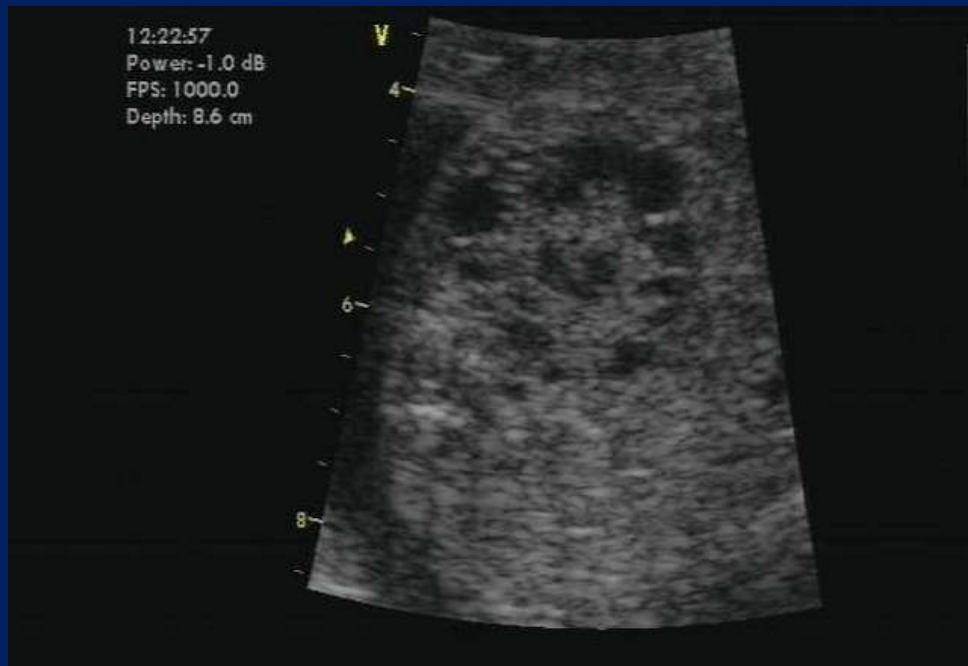
Nasal Bone absence

Provided by Miroslav Břešťák, MD,
PRONATAL sanatorium



Polycystic Kidney

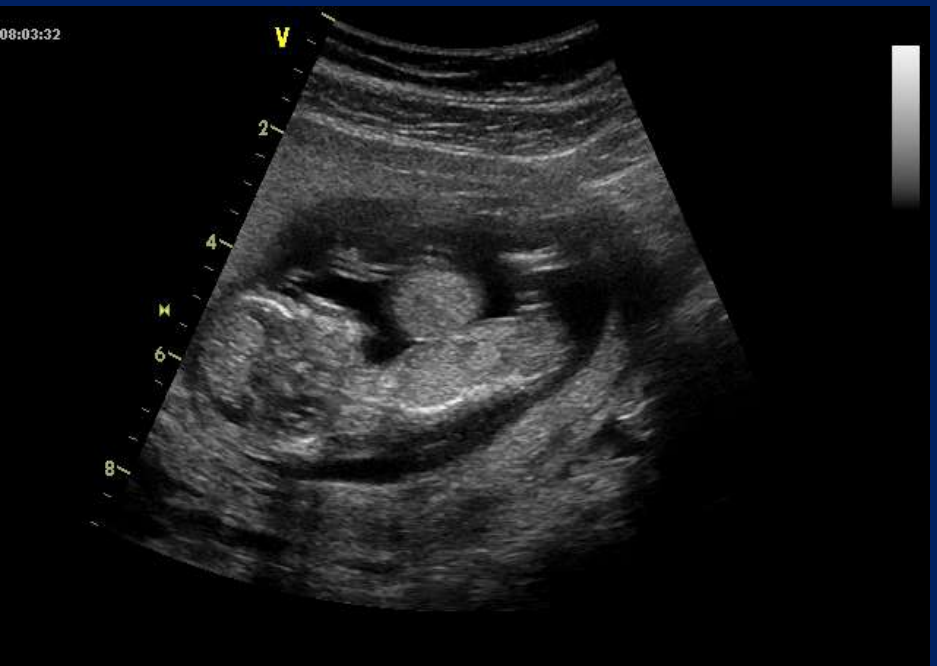
Provided by Miroslav Břešťák, MD,
PRONATAL sanatorium



USG images III

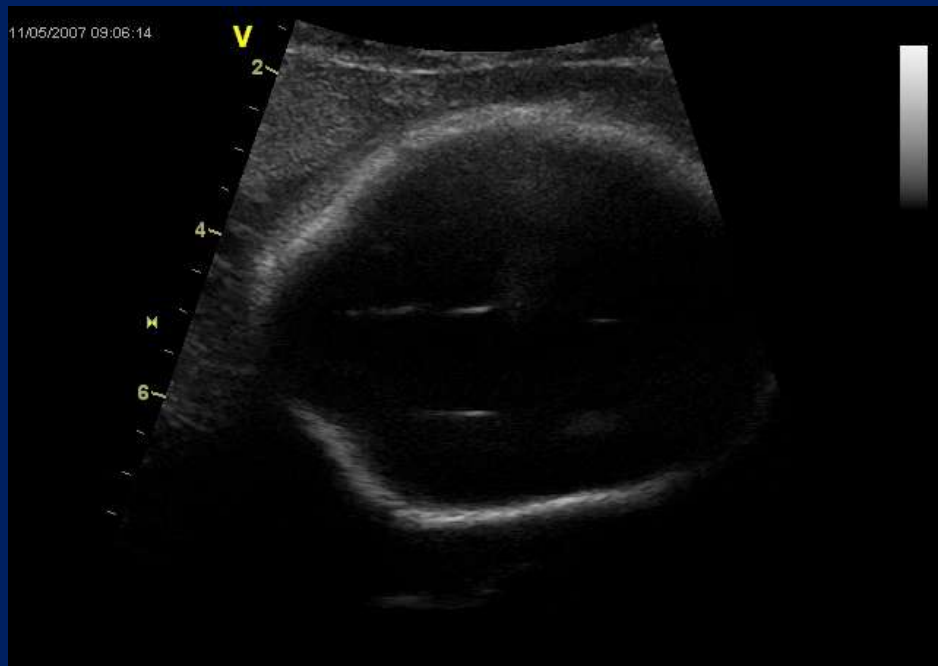
Exomphalos

Provided by Miroslav Břešťák, MD,
PRONATAL sanatorium



Rachischisis – lemon sign

Provided by Miroslav Břešťák, MD,
PRONATAL sanatorium



Prenatal diagnosis VIII

Preimplantation genetic diagnostics

PGD is a special method that is used during In Vitro Fertilization process. The material for diagnosis (either cytogenetic or molecular-genetic) is obtained before the embryo is implanted (one blastomere or a polar body may be used for this diagnosis).

This method may be extremely useful for parents with balanced chromosomal translocations or for parents who are carriers of severe genetic diseases (e.g. muscular dystrophies).

Only the embryos with normal karyotype / without genetic mutation shall be implanted.

However, there can be problem with blastomeric mosaicism, that can cause false-positive or false-negative results.

Prenatal diagnosis

History of prenatal diagnosis

Prenatal diagnosis in the Czech Republic

1970 – cultivation of the amniocytes
1971 – first prenatally diagnosed Down Syndrome
1977 – placentocentesis
1978 – fetoscopy
1980 – ultrasound diagnostics
1983 – CVS
1985 – prenatal molecular-genetic analysis – hemophilia
1987 – cordocentesis
1988 – early amniocentesis
1990 – prenatal biochemical screening
2000 – preimplantation genetic diagnostics (PGD)

Congenital anomalies

1. Definitions
2. Etiology, teratogens
3. Selected congenital anomalies
4. Prenatal diagnosis
5. Incidence of selected congenital anomalies
6. Summary

Population teratology

Definitions

Population teratology analyses the **mean incidences** of congenital anomalies (CAs) in selected population. Long, consensual monitoring is necessary in order to find any **trends** that may appear in the incidence of some congenital anomalies (either increase or decrease).

Other findings may be **accumulation** of CAs, **clustering** of CAs, **cyclic changes** in the incidence of CAs, or so called **nesting**.

Incidence I

Czech Republic

History of **Congenital Anomalies Monitoring Program of Czech Republic** is very long. The regular monitoring started in **1964**. The registration itself undergo many changes during more than 40 years of existence.

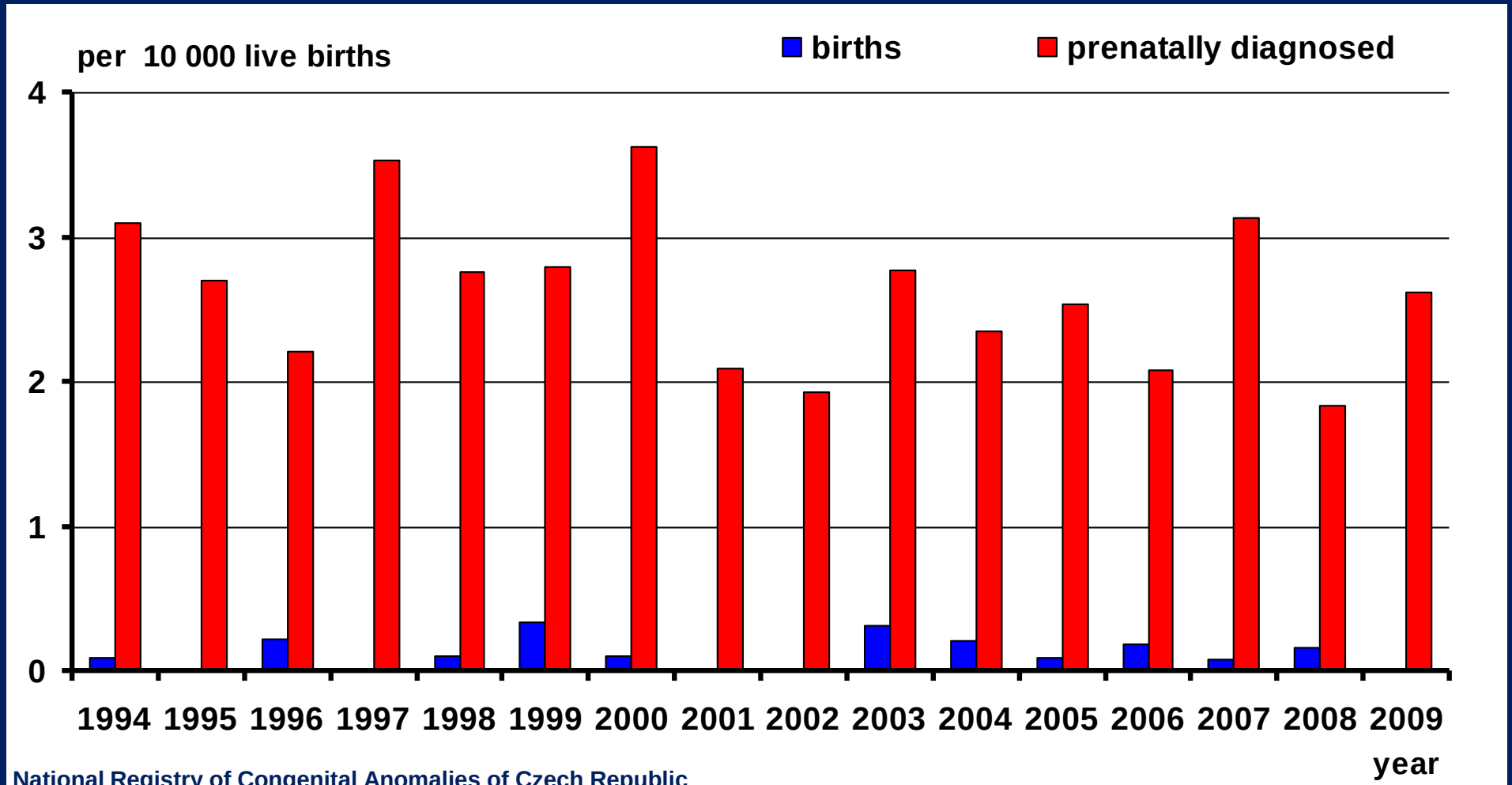
Currently we register any diagnosis from ICD-X **Q00-Q99** group, that was diagnosed prenatally or postnatally until (finished) **15th year** of live.

The data for the registry are collected in the **Institute of Health Information and Statistics of the Czech Republic** (ÚZIS ČR).

The Czech Registry was one of founding members of **ICBDSR** (International Clearinghouse for Birth Defects Surveillance and Research) international organization.

Incidence II

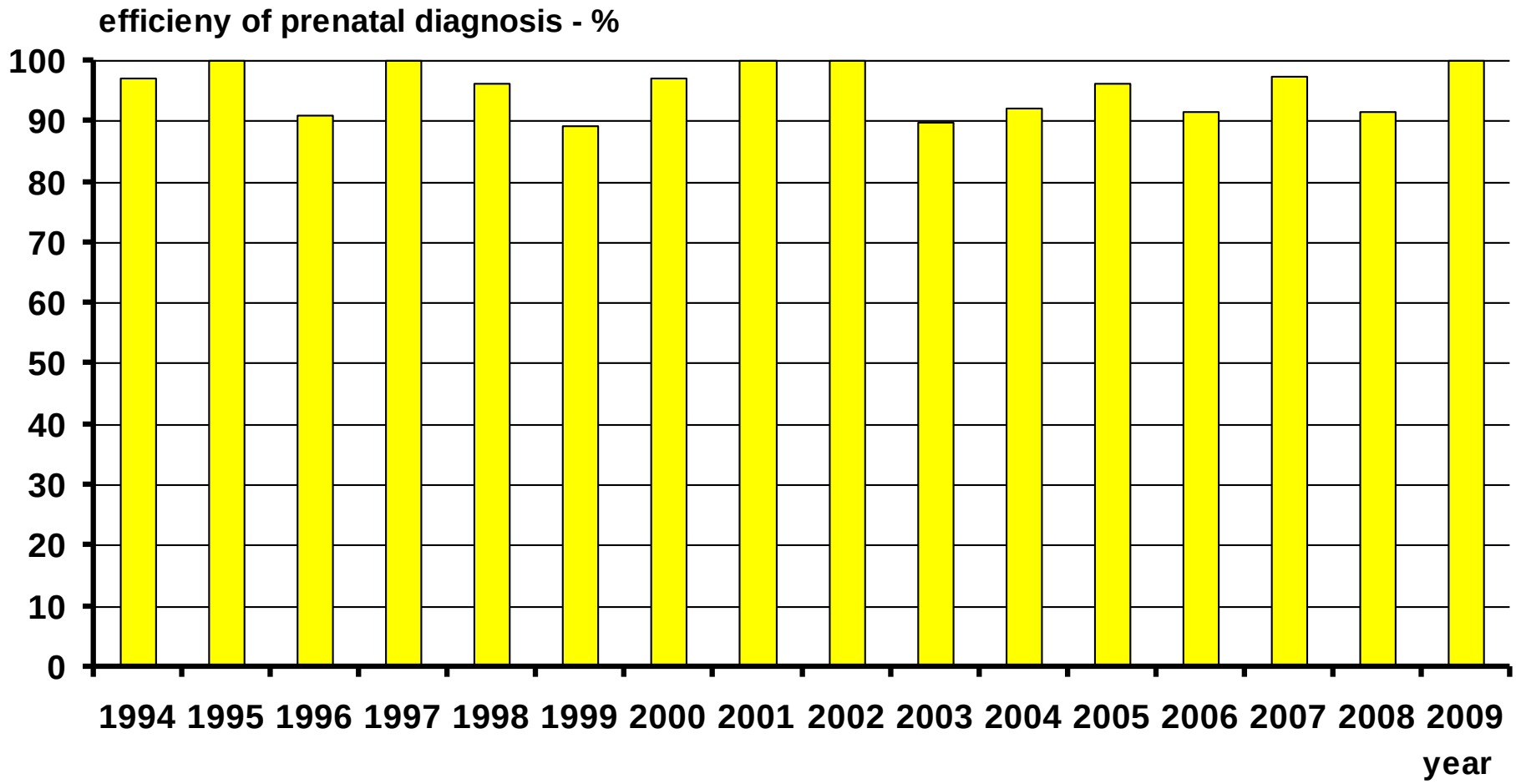
Anencephaly in Czech Republic 1994 - 2009



National Registry of Congenital Anomalies of Czech Republic

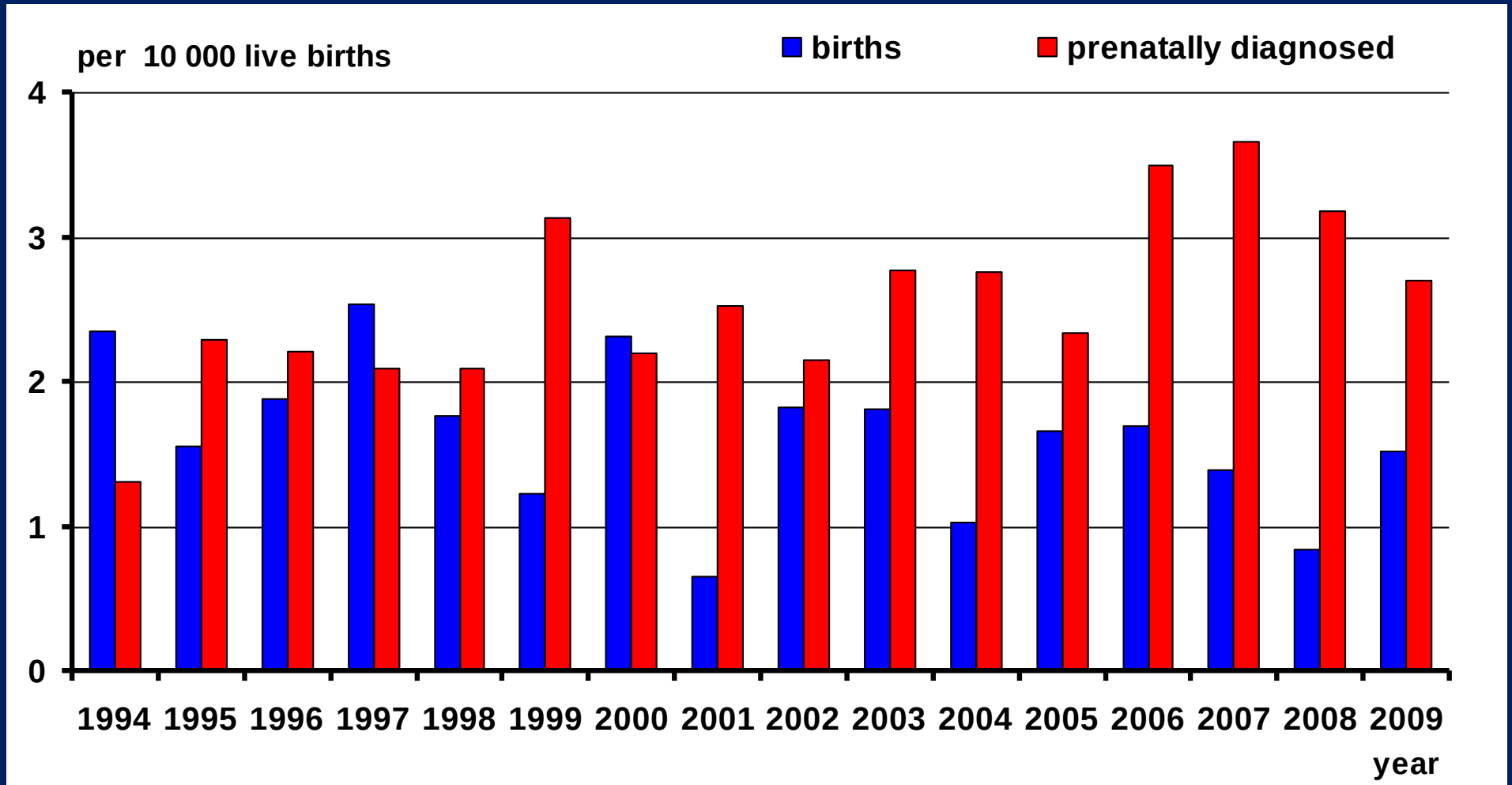
Incidence III

Anencephaly in Czech Republic 1994 - 2009



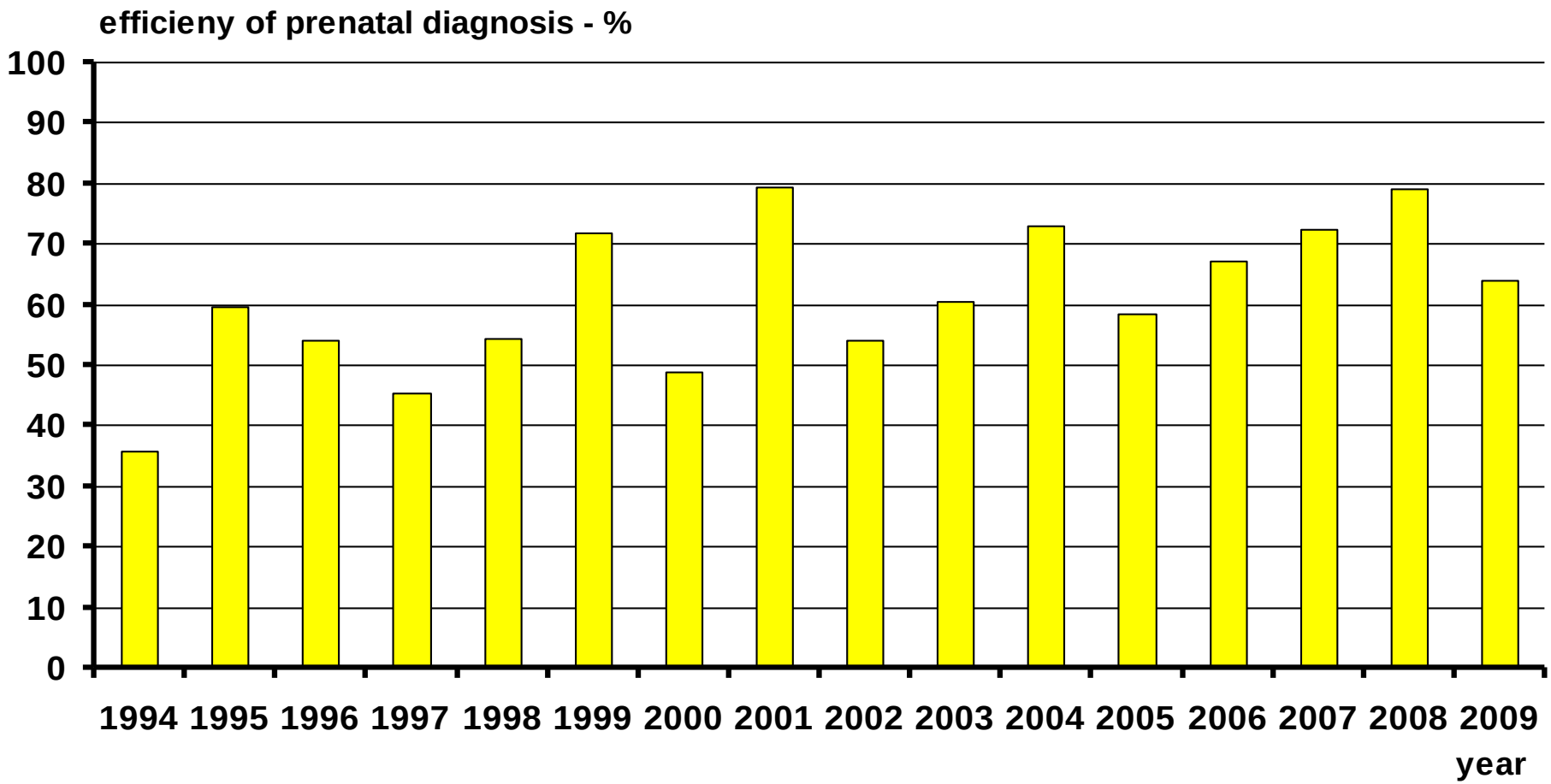
Incidence IV

Spina Bifida in Czech Republic 1994 - 2009



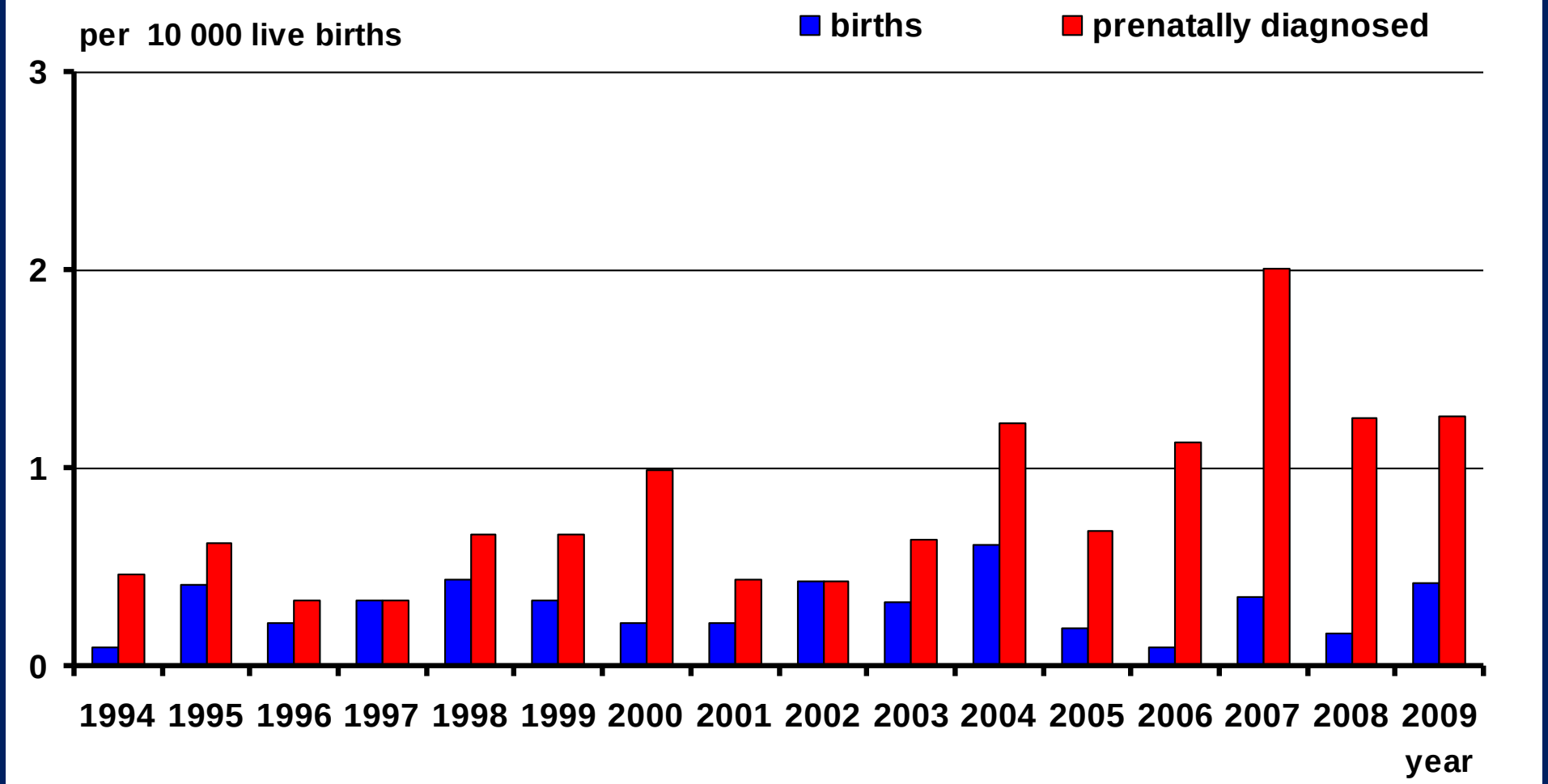
Incidence V

Spina Bifida in Czech Republic 1994 - 2009



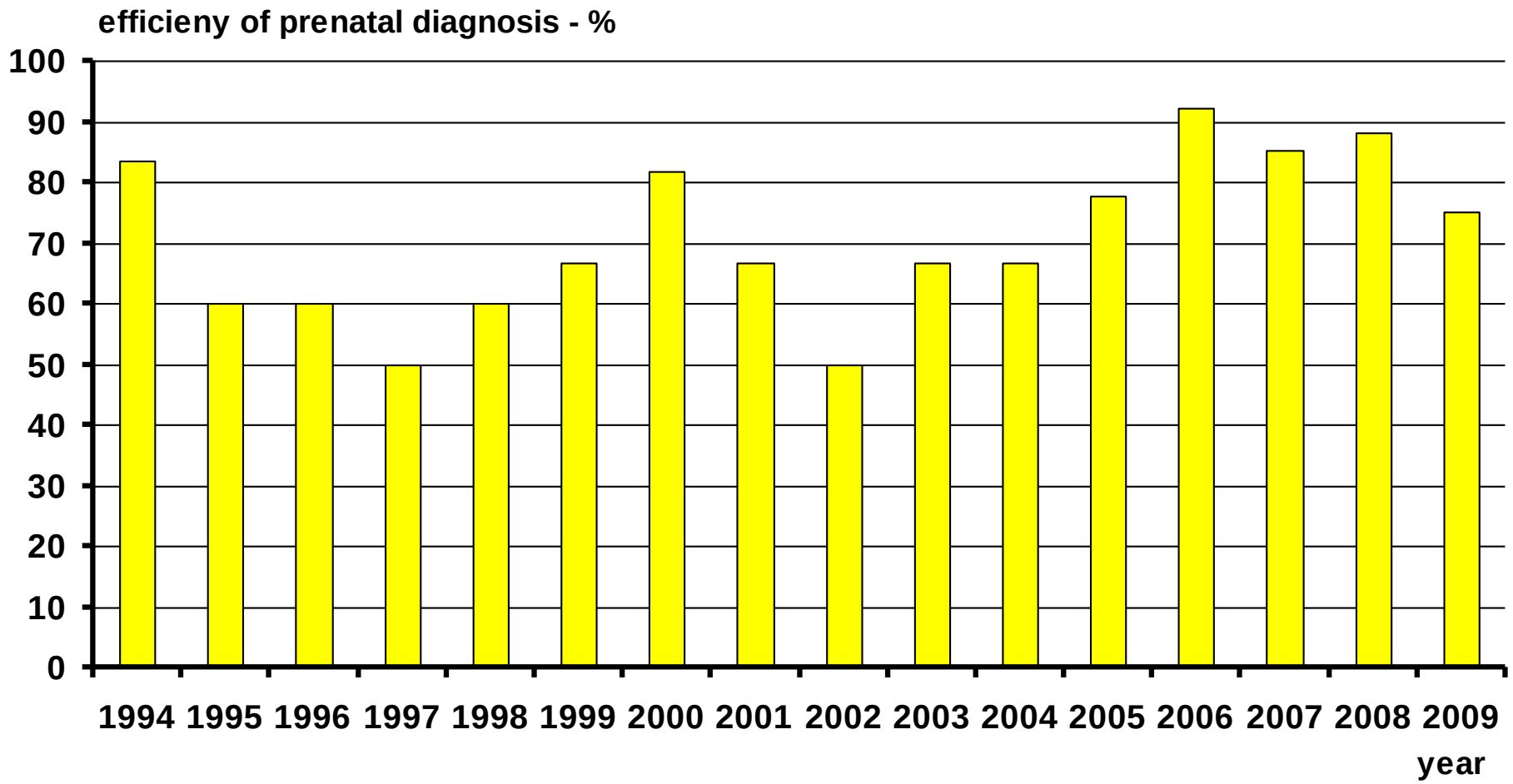
Incidence VI

Encephalocele in Czech Rep. 1994 - 2009



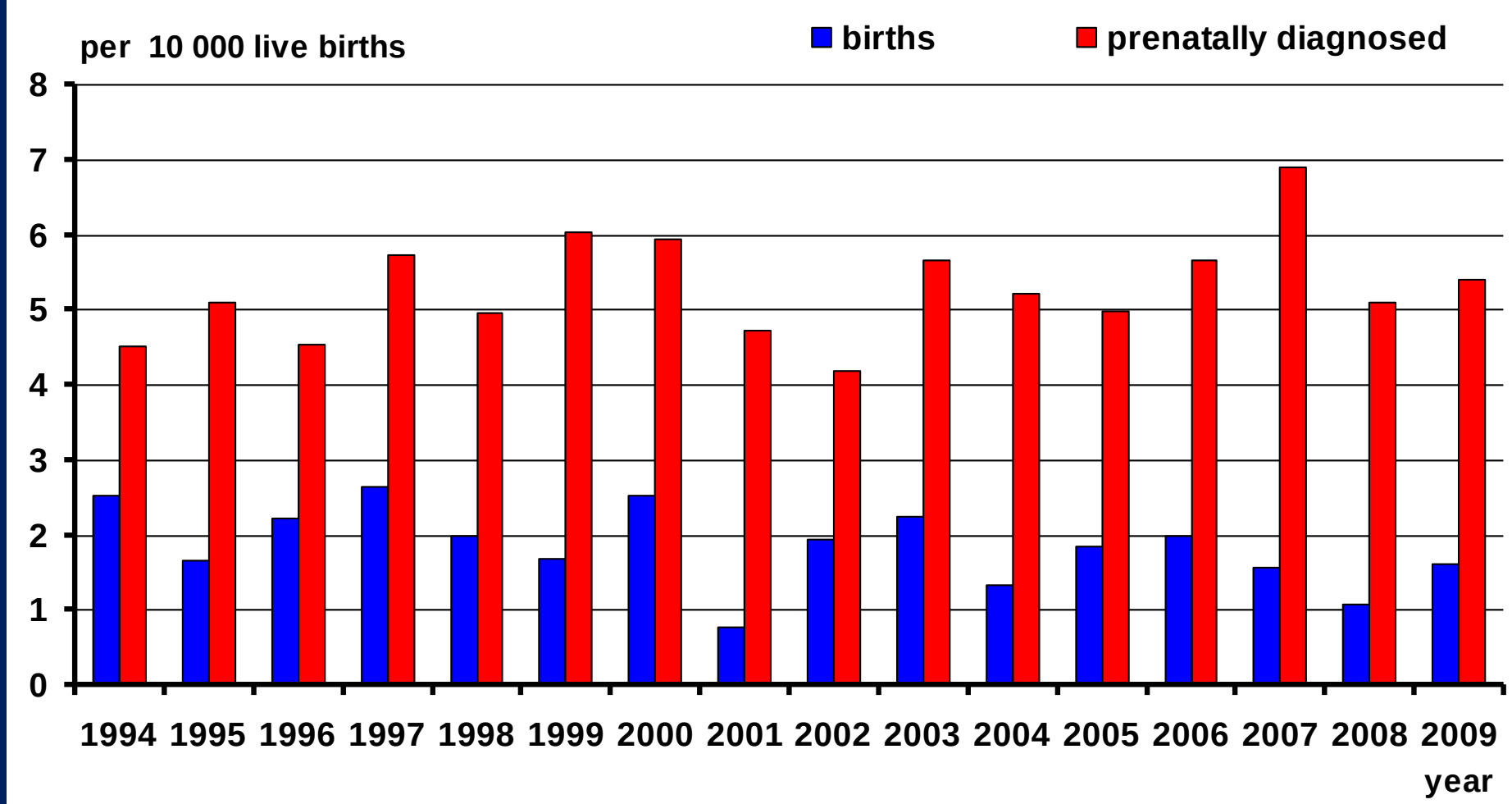
Incidence VII

Encephalocele in Czech Rep. 1994 - 2009



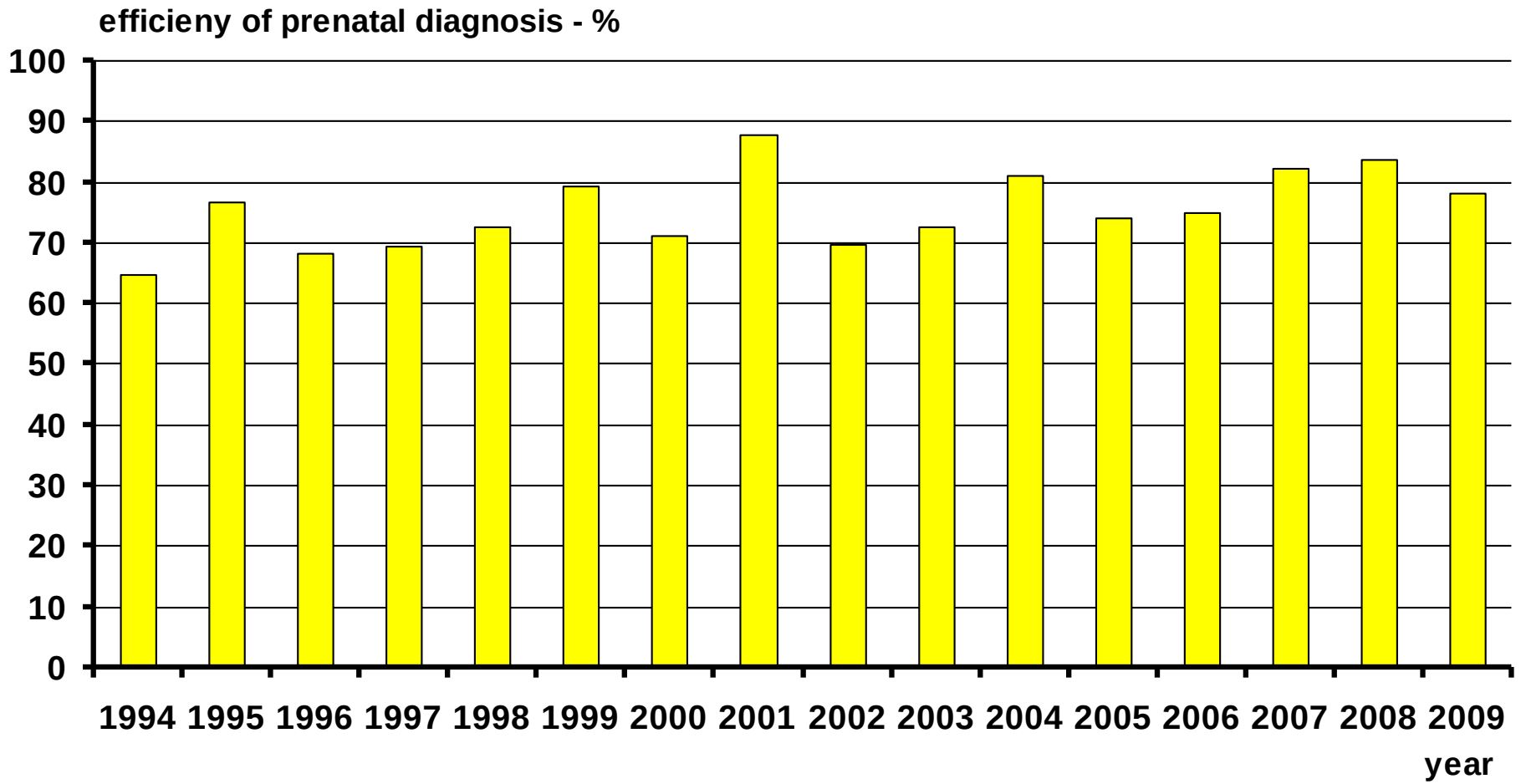
Incidence VIII

NTD together, Czech Republic 1994 - 2009



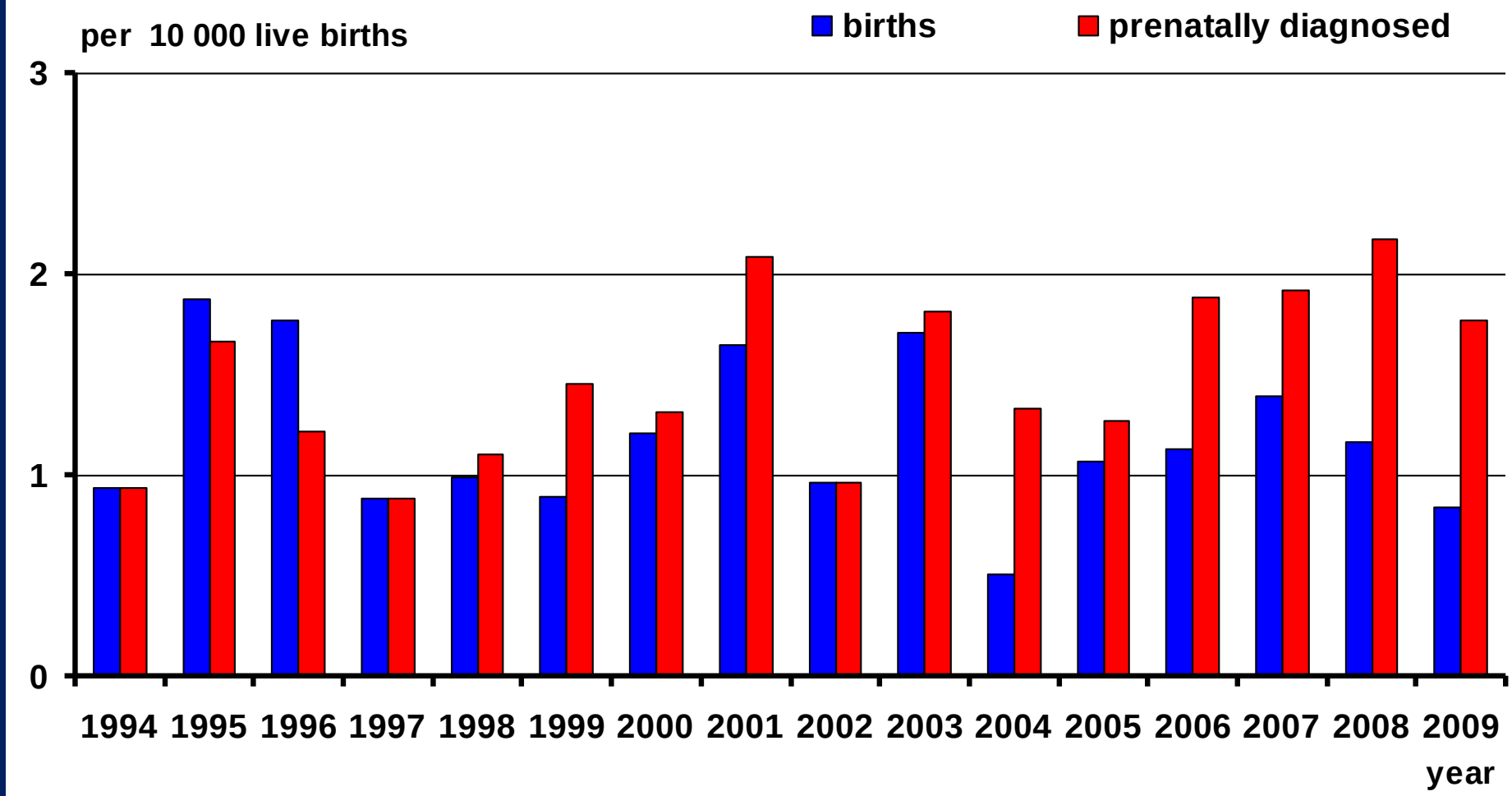
Incidence IX

NTD together, Czech Republic 1994 - 2009



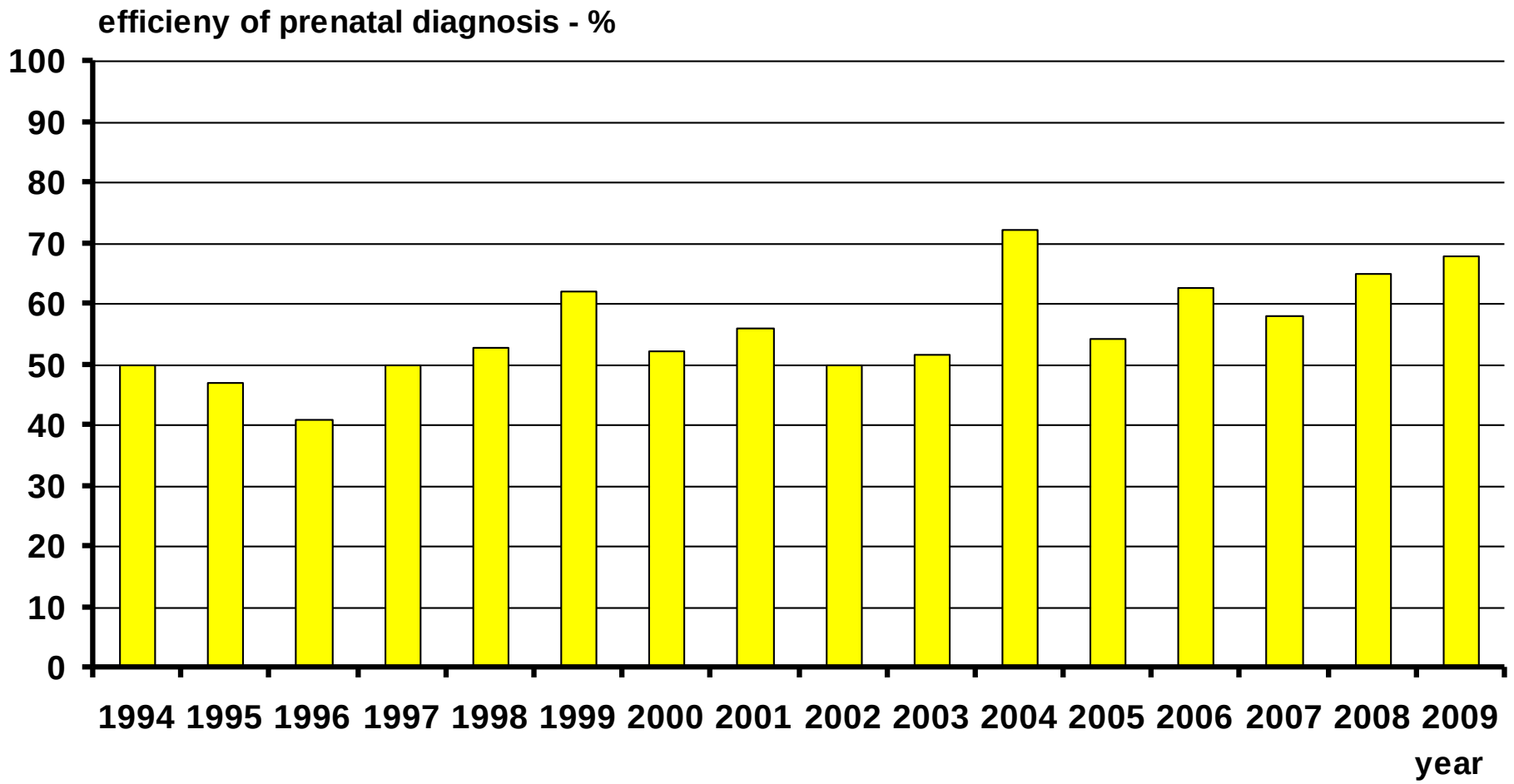
Incidence X

Omphalocele in Czech Republic 1994 - 2009



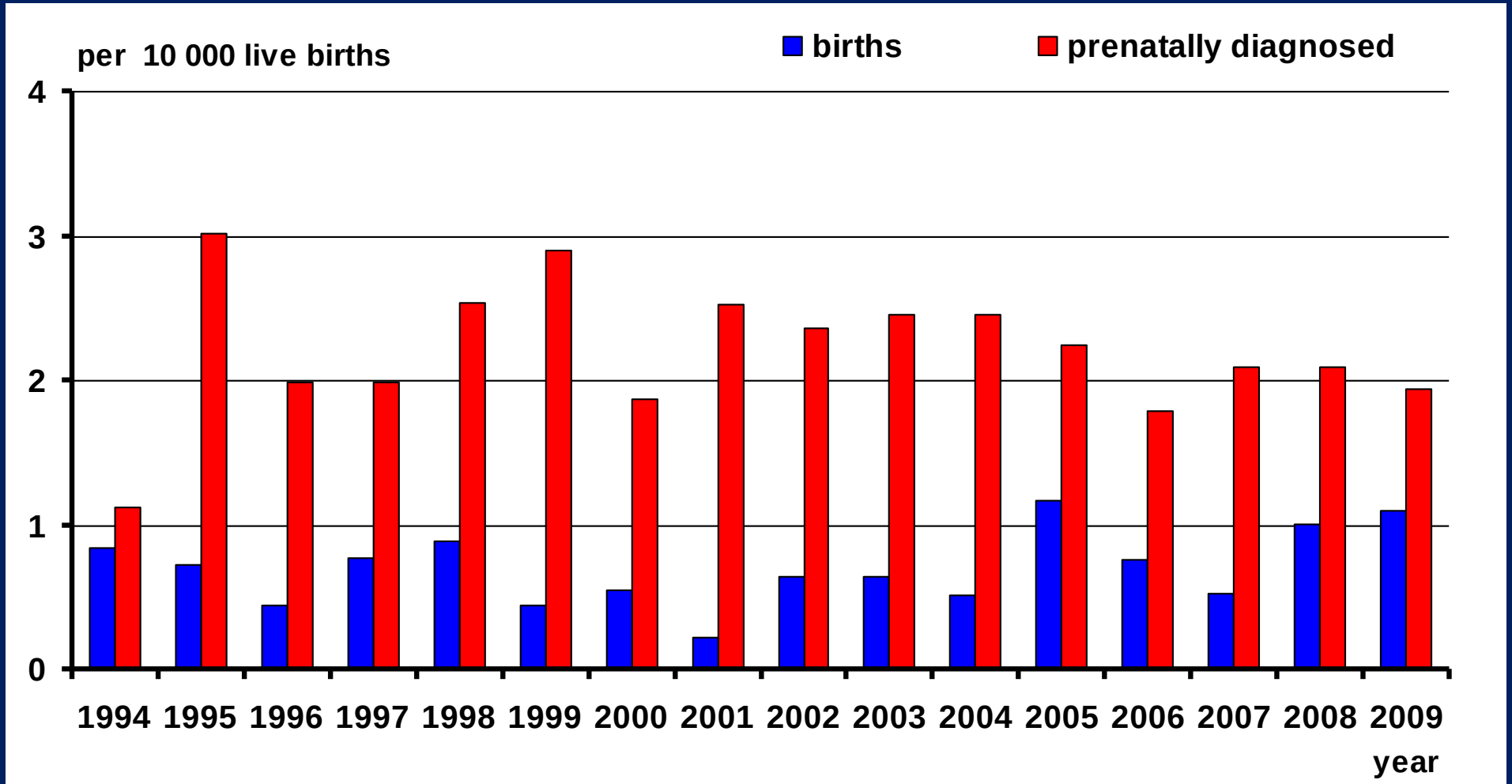
Incidence XI

Omphalocele in Czech Republic 1994 - 2009



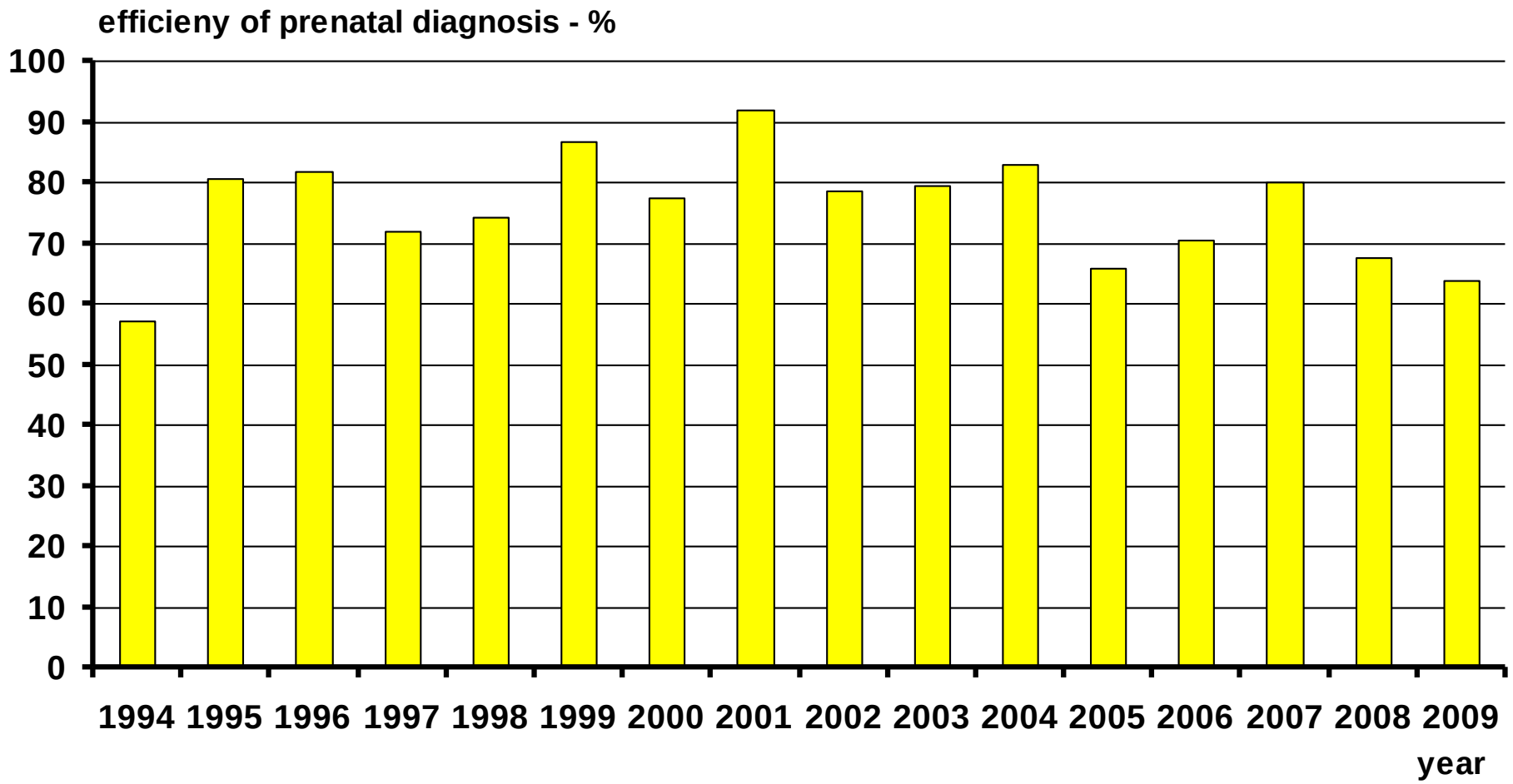
Incidence XII

Gastroschisis in Czech Republic 1994 - 2009



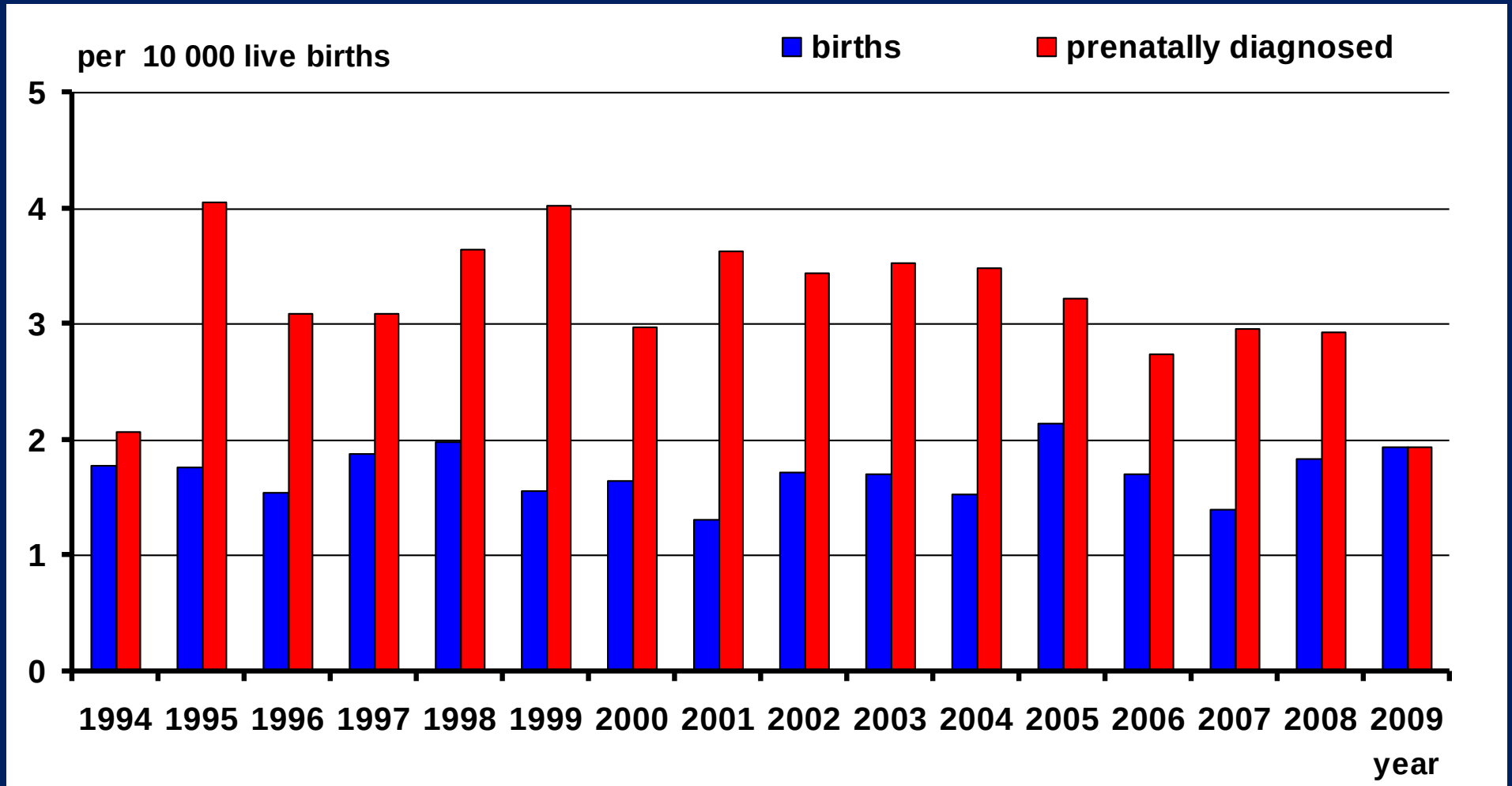
Incidence XIII

Gastroschisis in Czech Republic 1994 - 2009



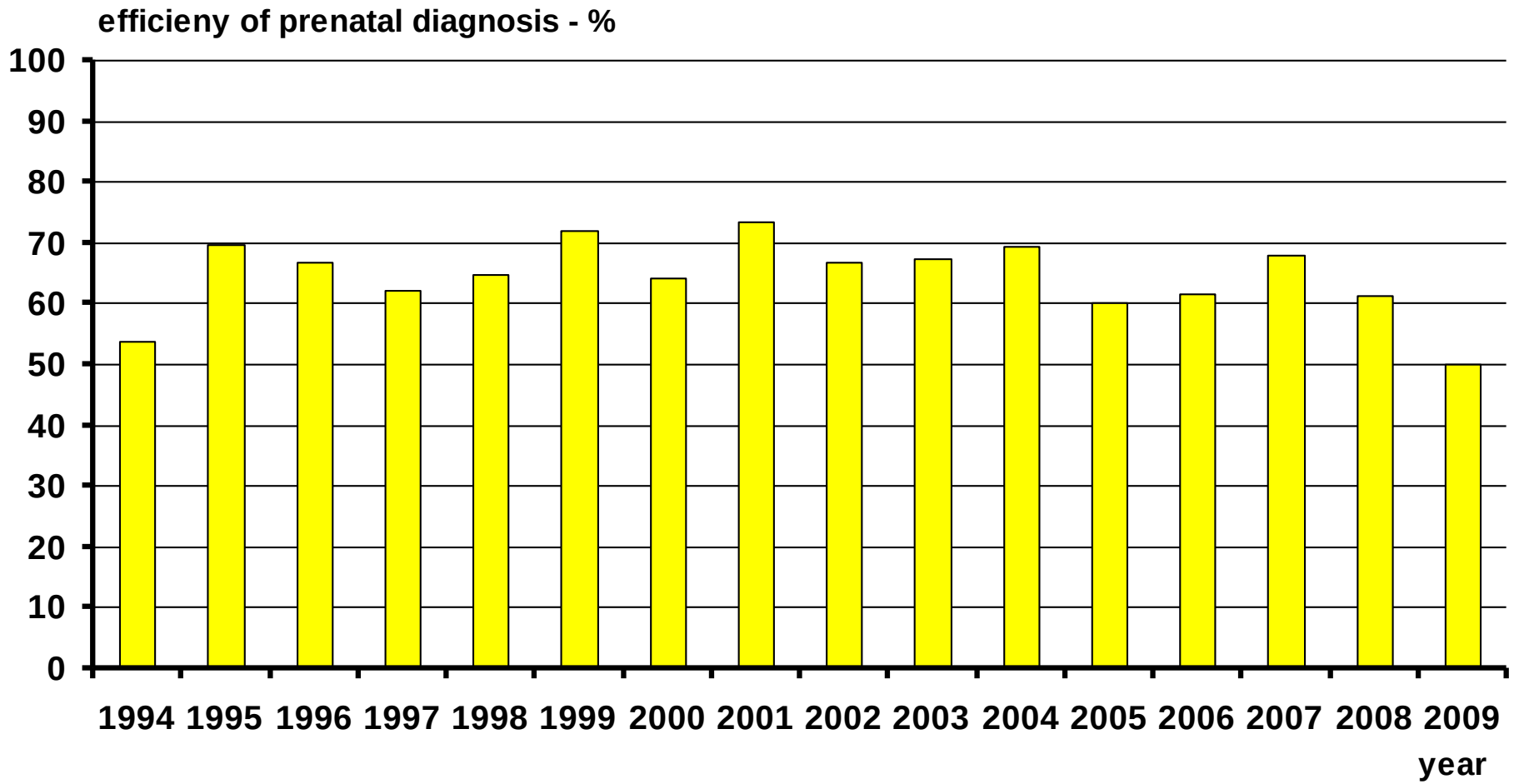
Incidence XIV

AWD in Czech Republic 1994 - 2009



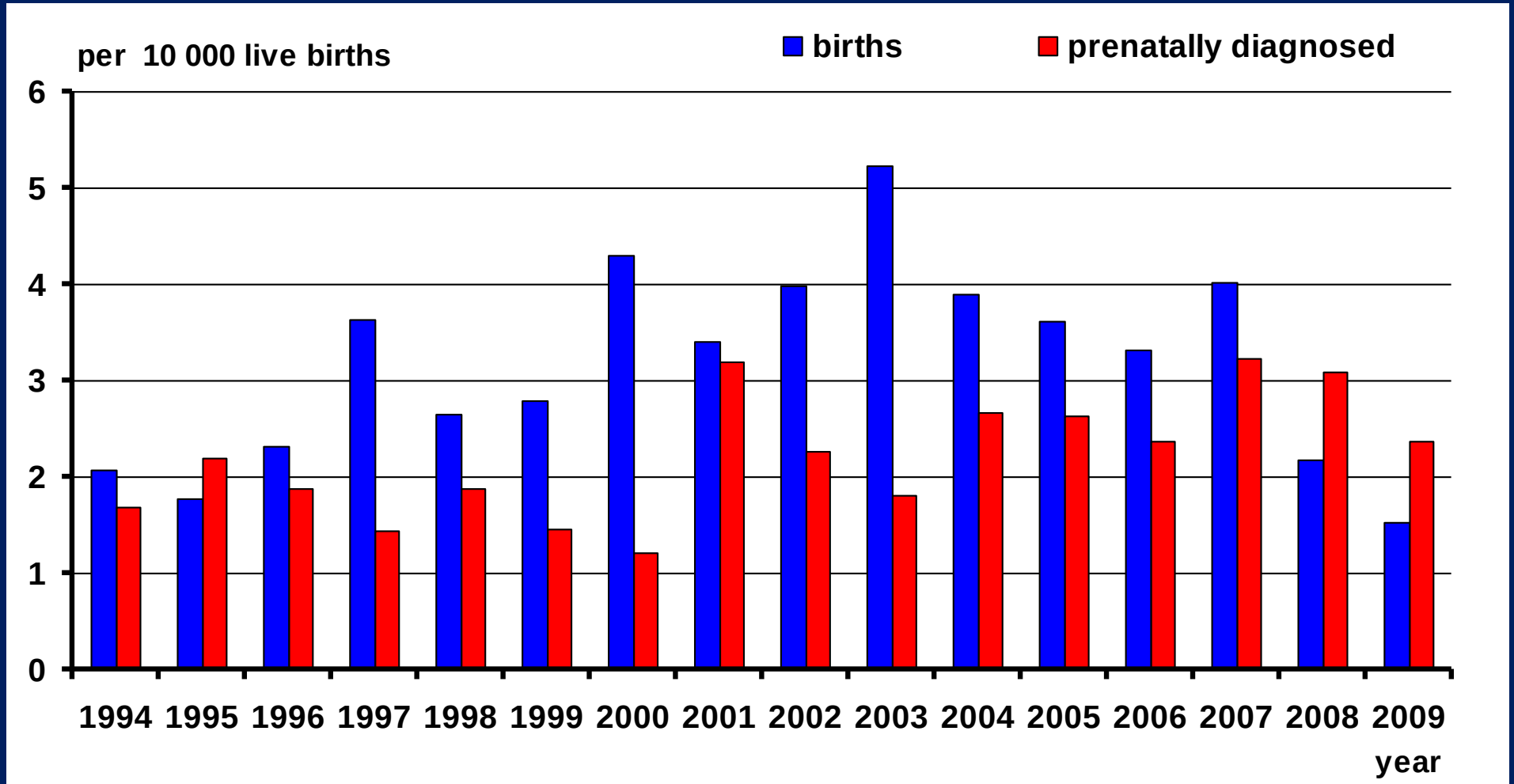
Incidence XV

AWD in Czech Republic 1994 - 2009



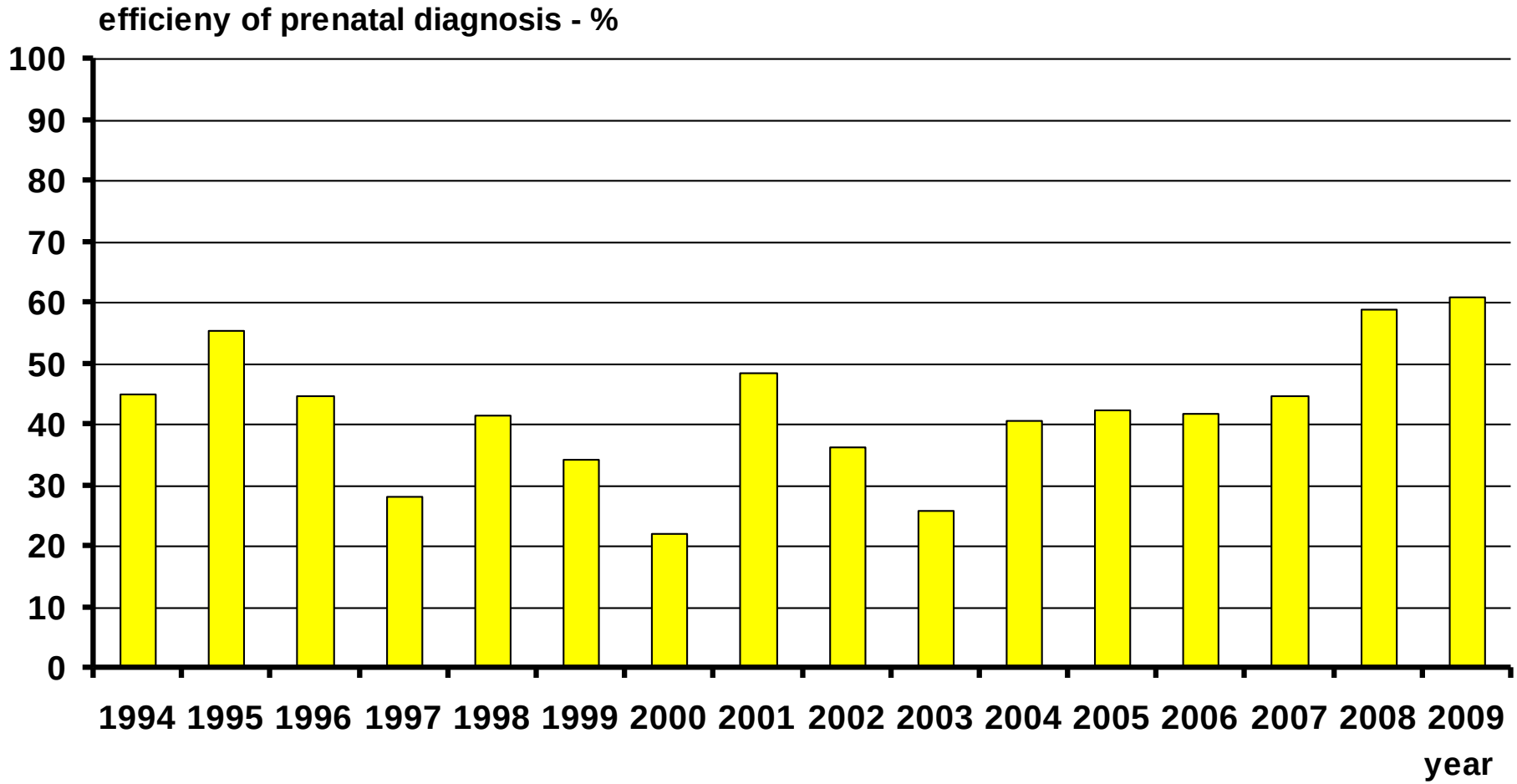
Incidence XVI

Hydrocephaly in Czech Rep. 1994 - 2009



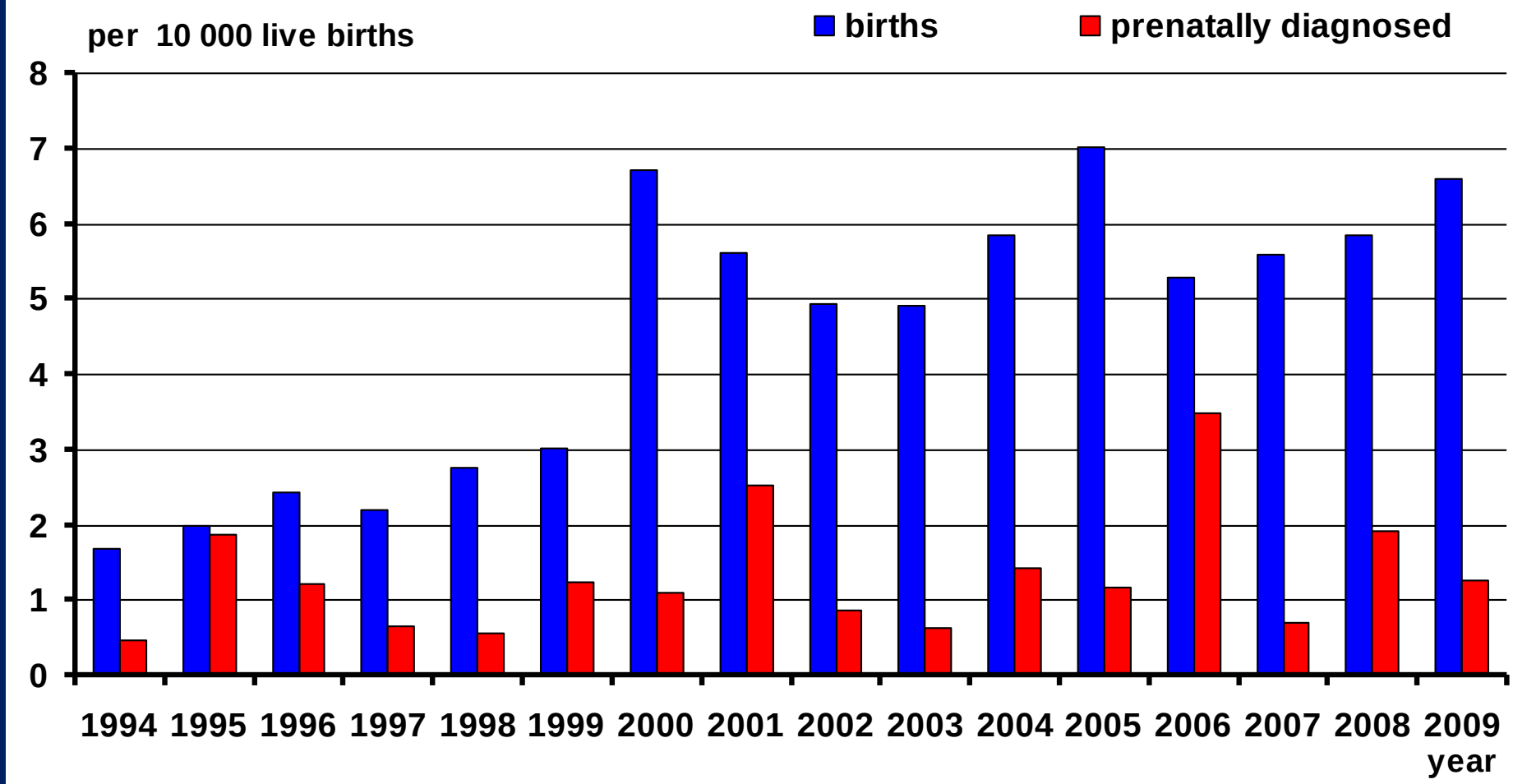
Incidence XVII

Hydrocephaly in Czech Rep. 1994 - 2009



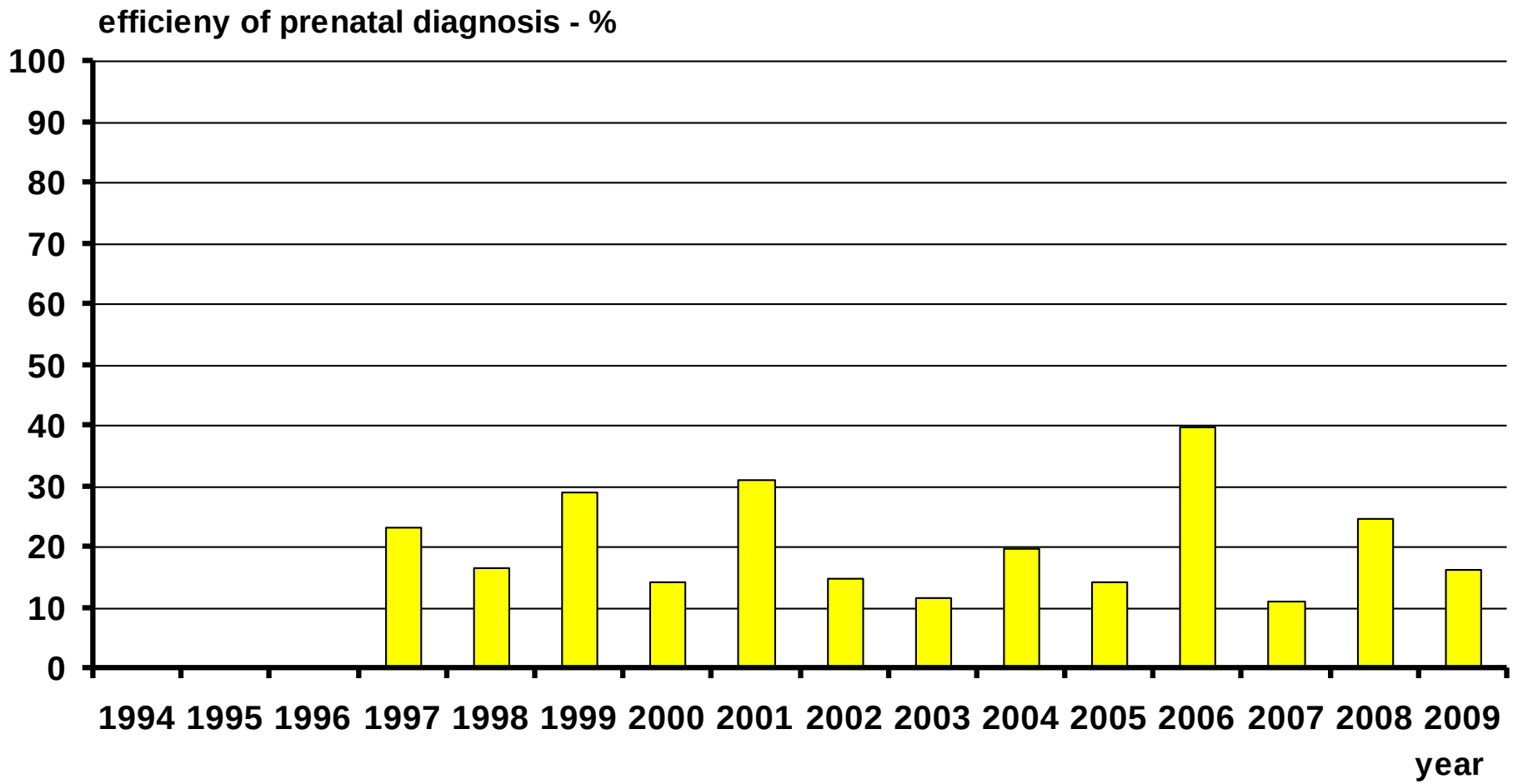
Incidence XVIII

Cystic kidney dis. in Czech Rep. 1994 - 2009



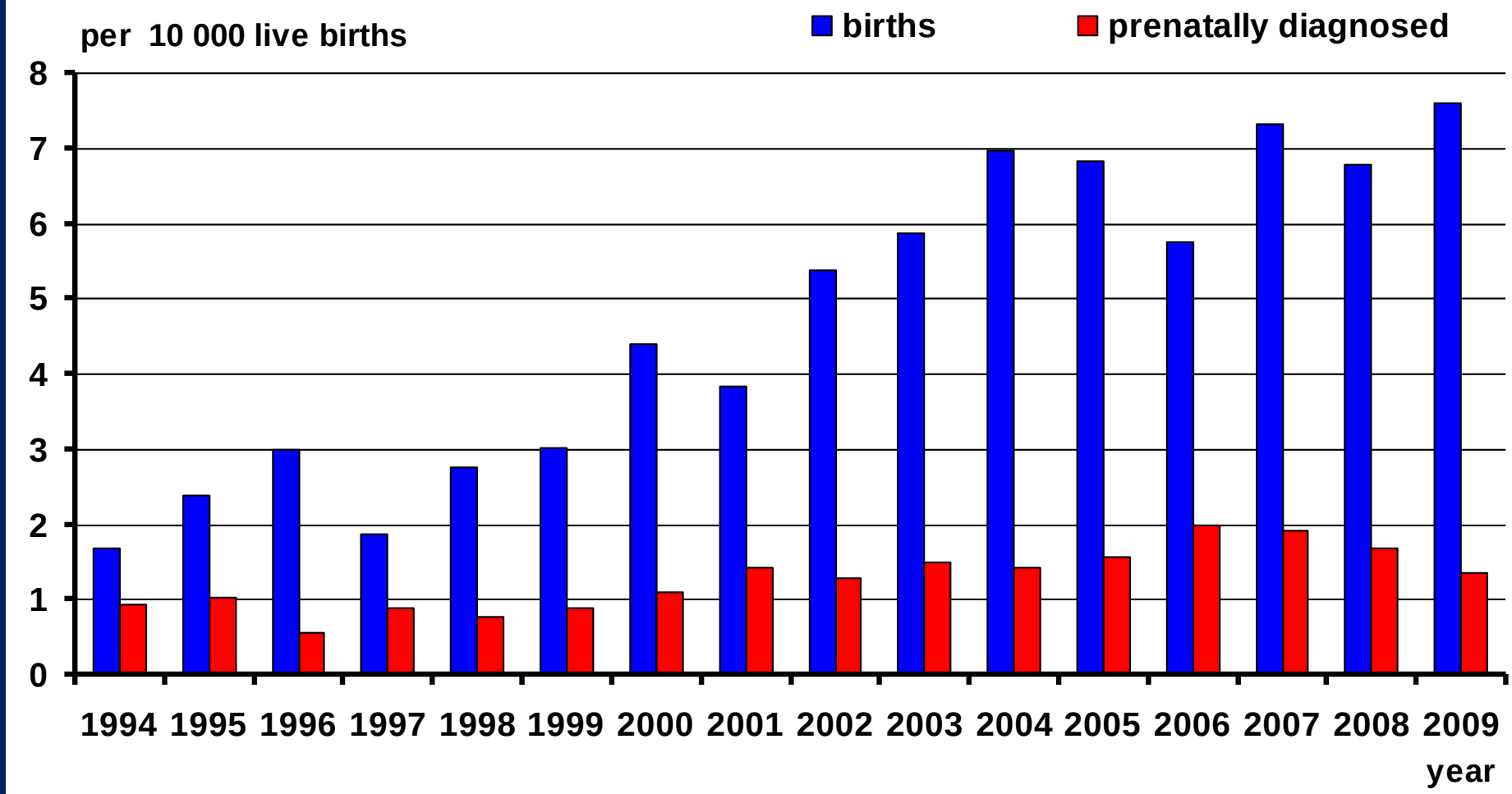
Incidence XIX

Cystic kidney dis. in Czech Rep. 1994 - 2009



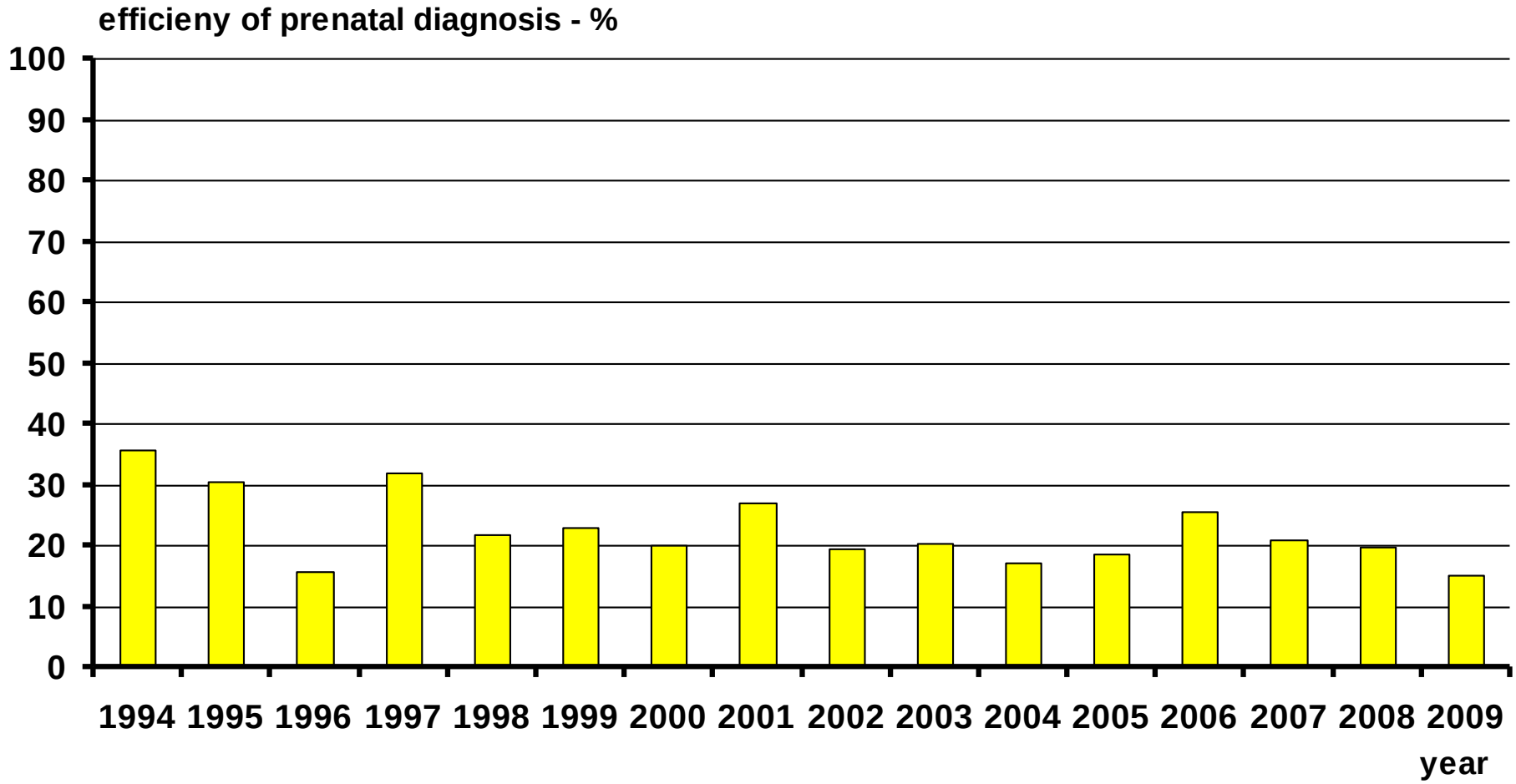
Incidence XX

Renal agenesis in Czech Rep. 1994 - 2009



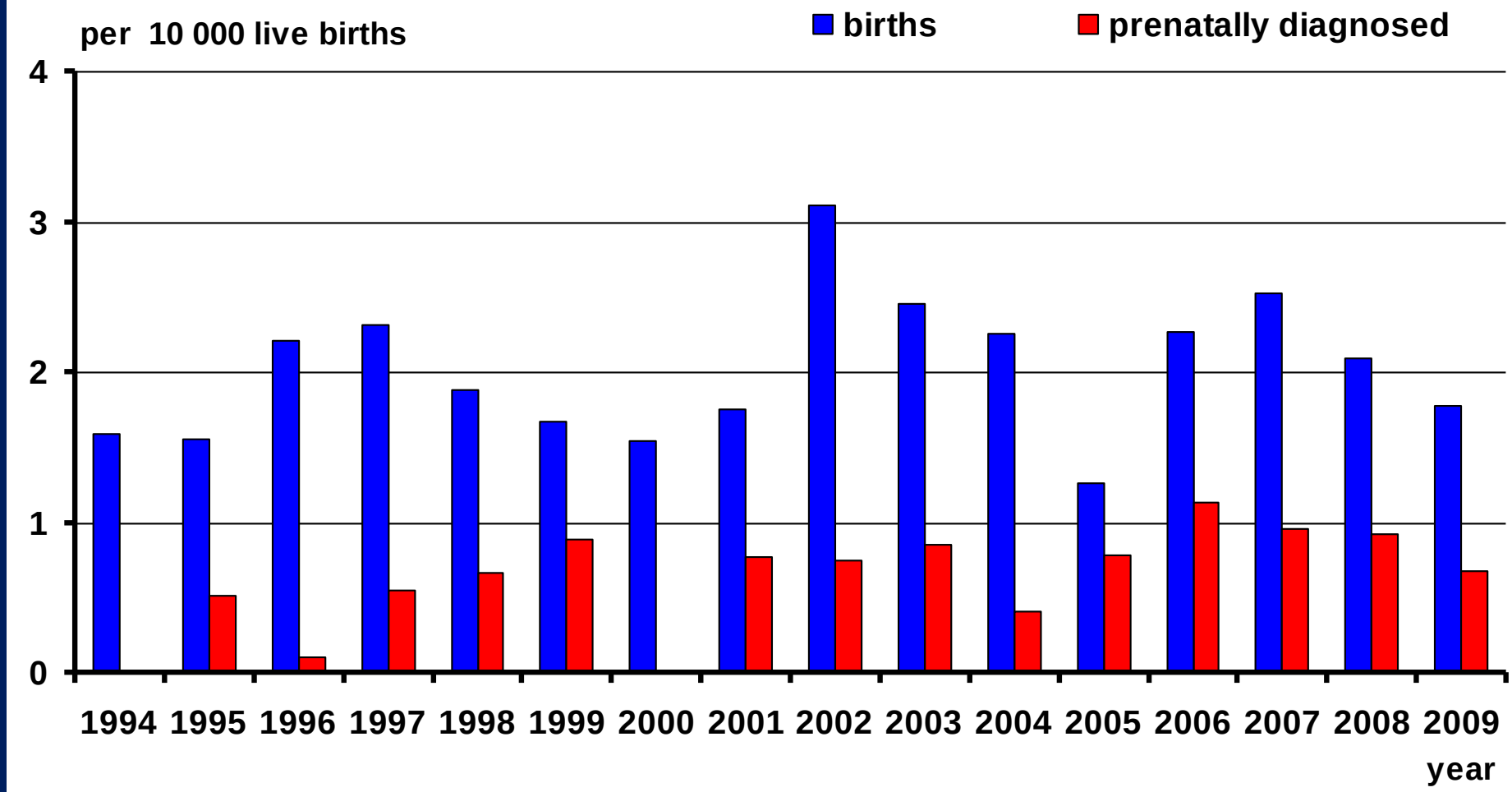
Incidence XXI

Renal agenesis in Czech Rep. 1994 - 2009



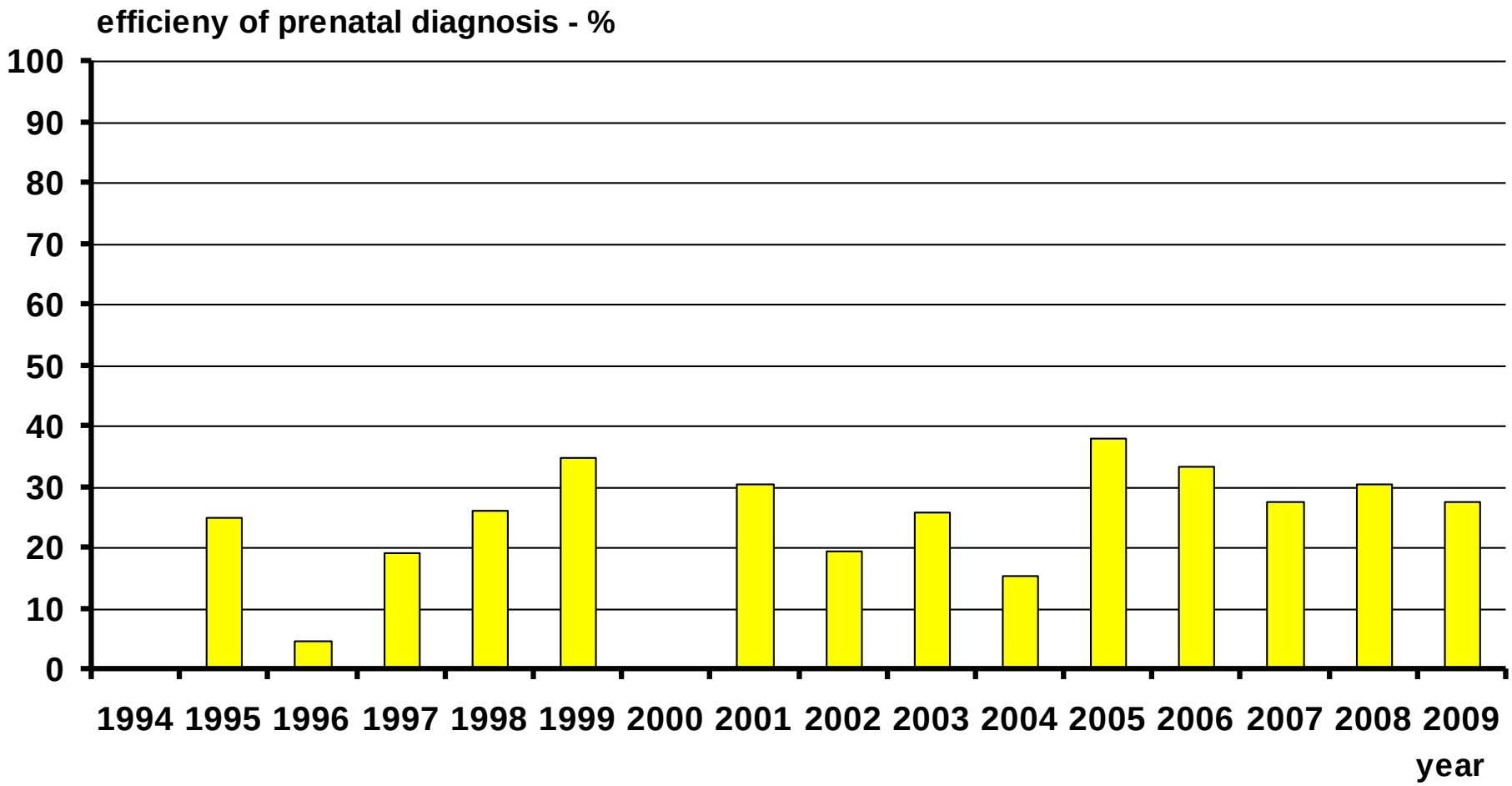
Incidence XXII

Diaphragm. hernia in Czech Rep. 1994 - 2009



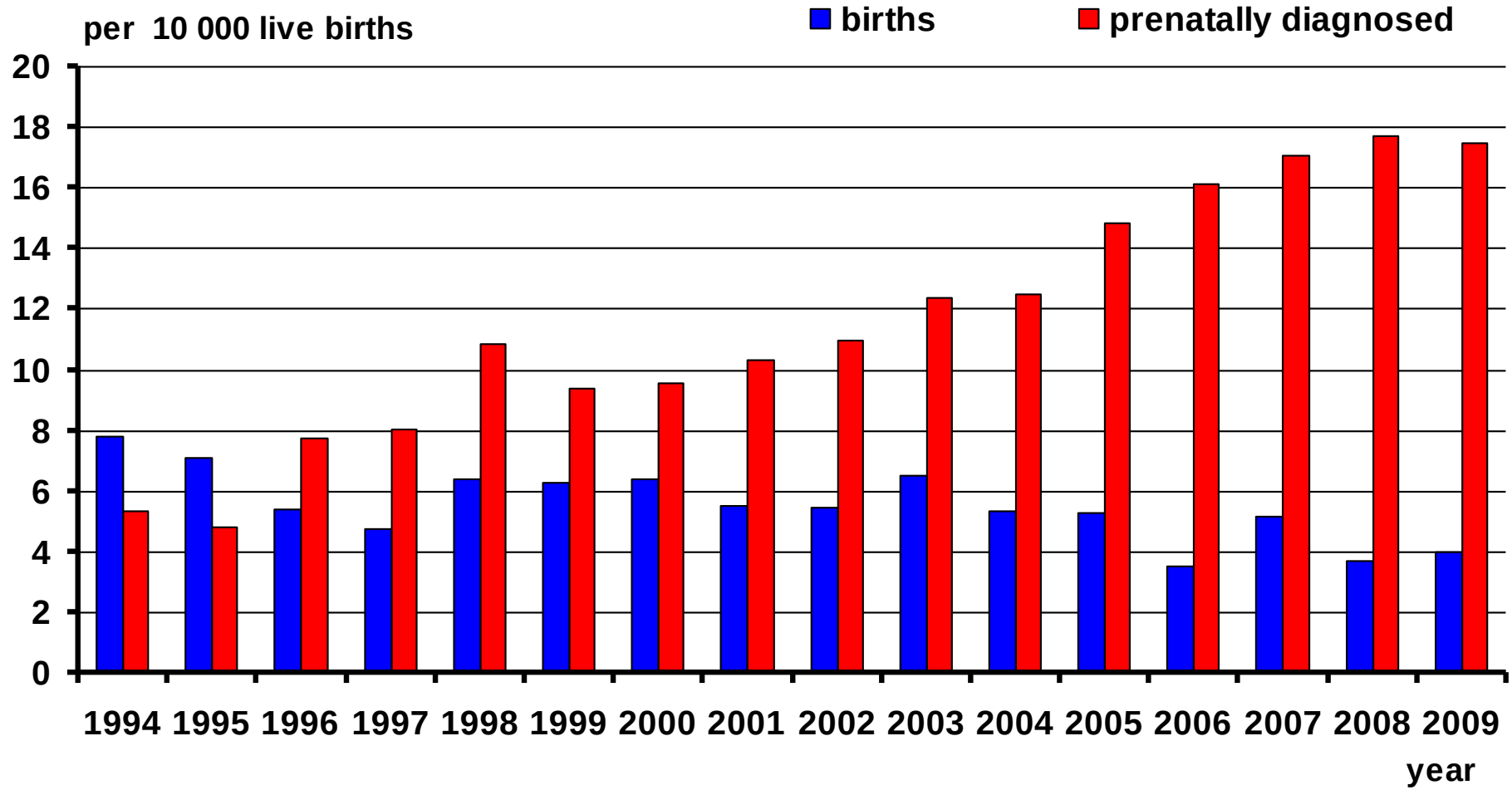
Incidence XXIII

Diaphragm. hernia in Czech Rep. 1994 - 2009



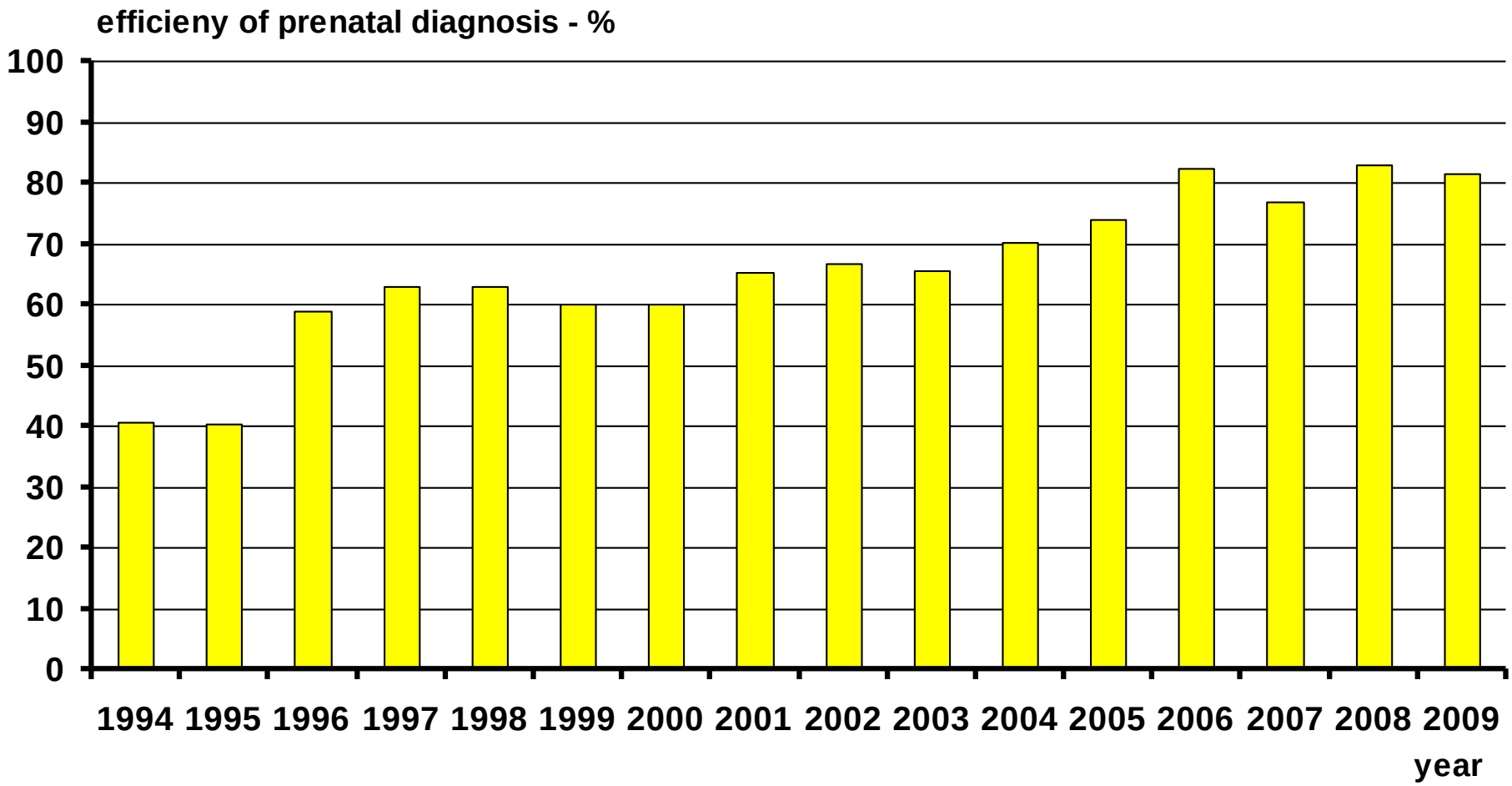
Incidence XXIV

Down Syndrome in Czech Rep. 1994 - 2008



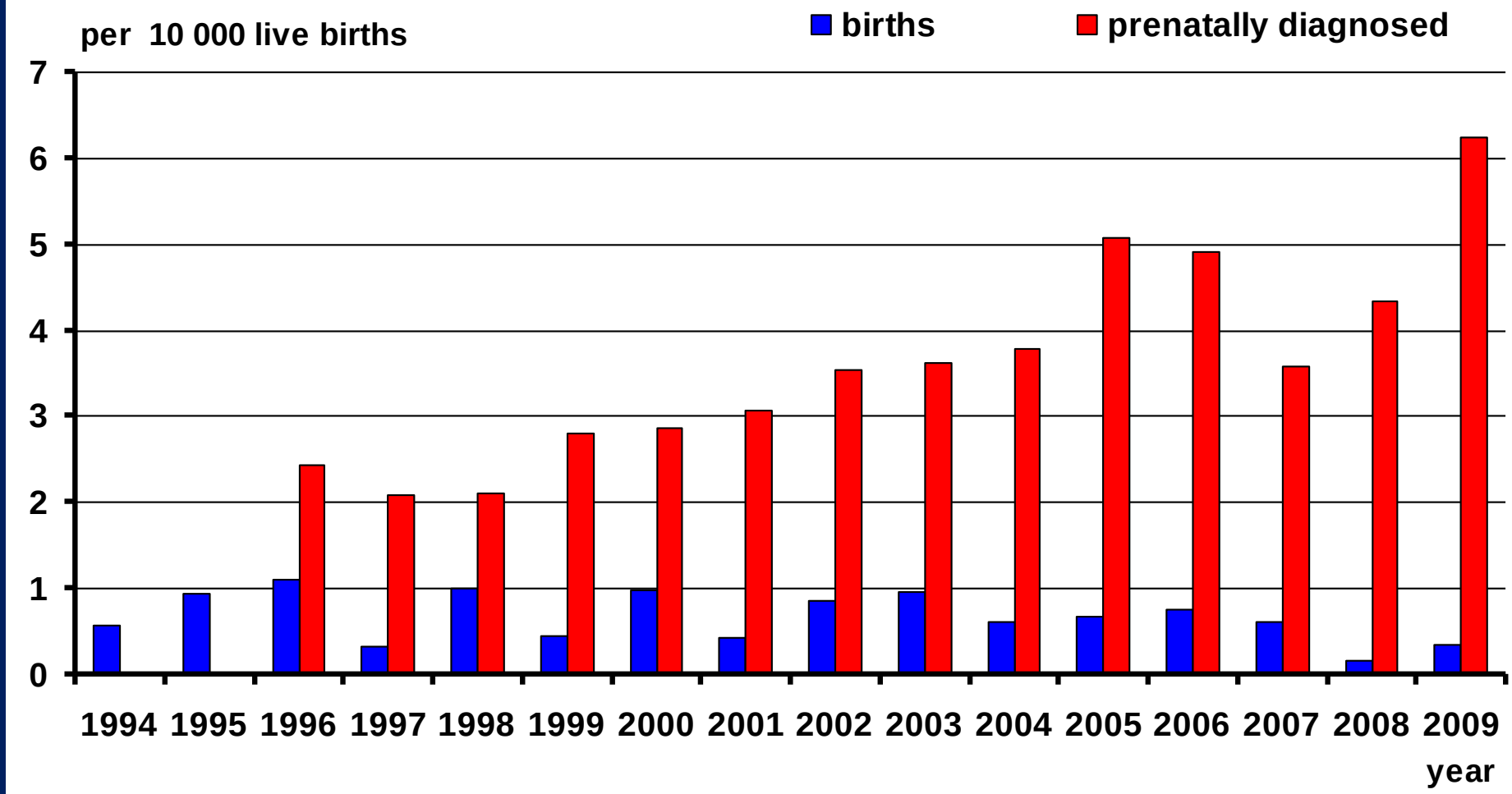
Incidence XXV

Down Syndrome in Czech Rep. 1994 - 2009



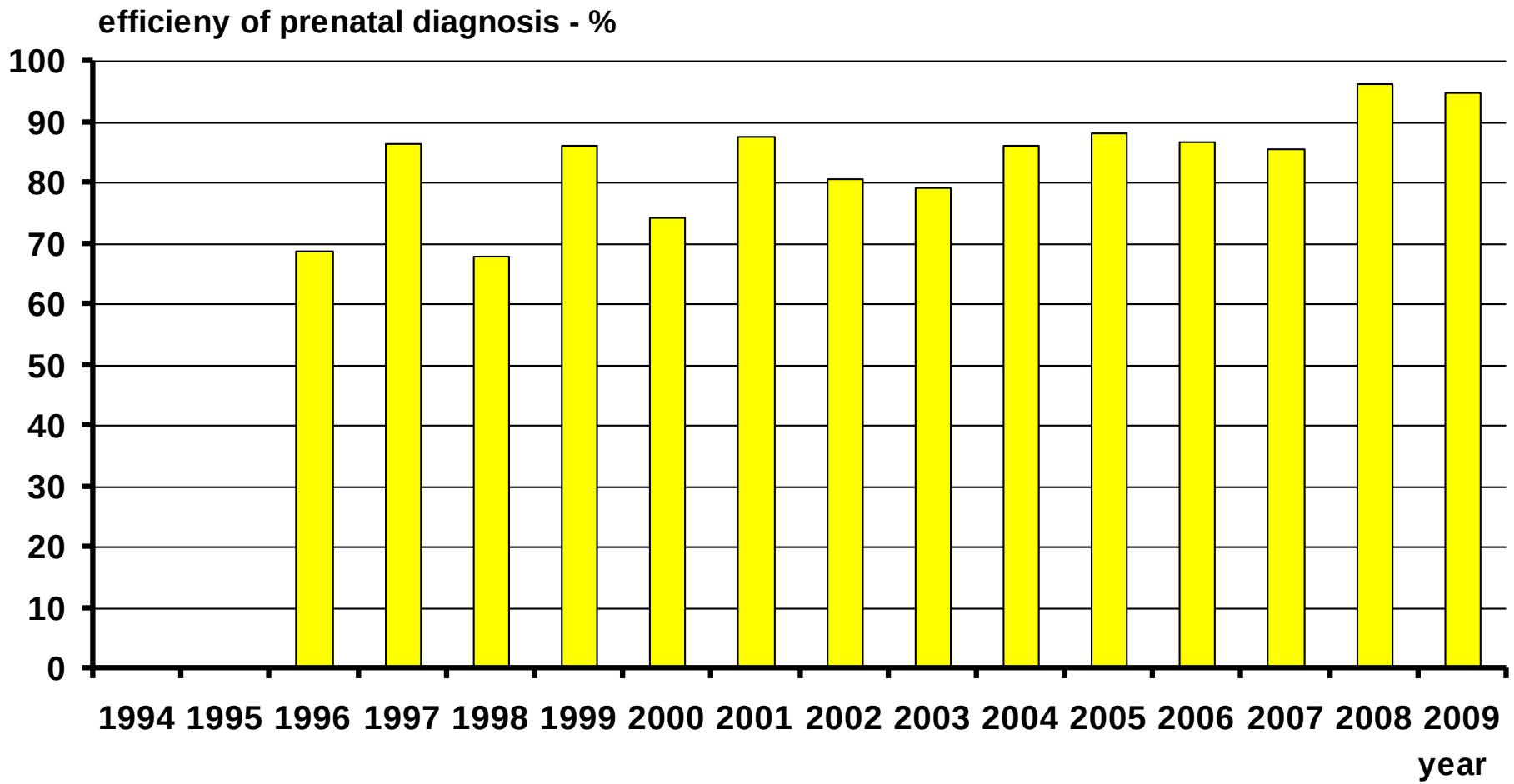
Incidence XXVI

Edwards Syndrome in Czech Rep. 1994 - 2009



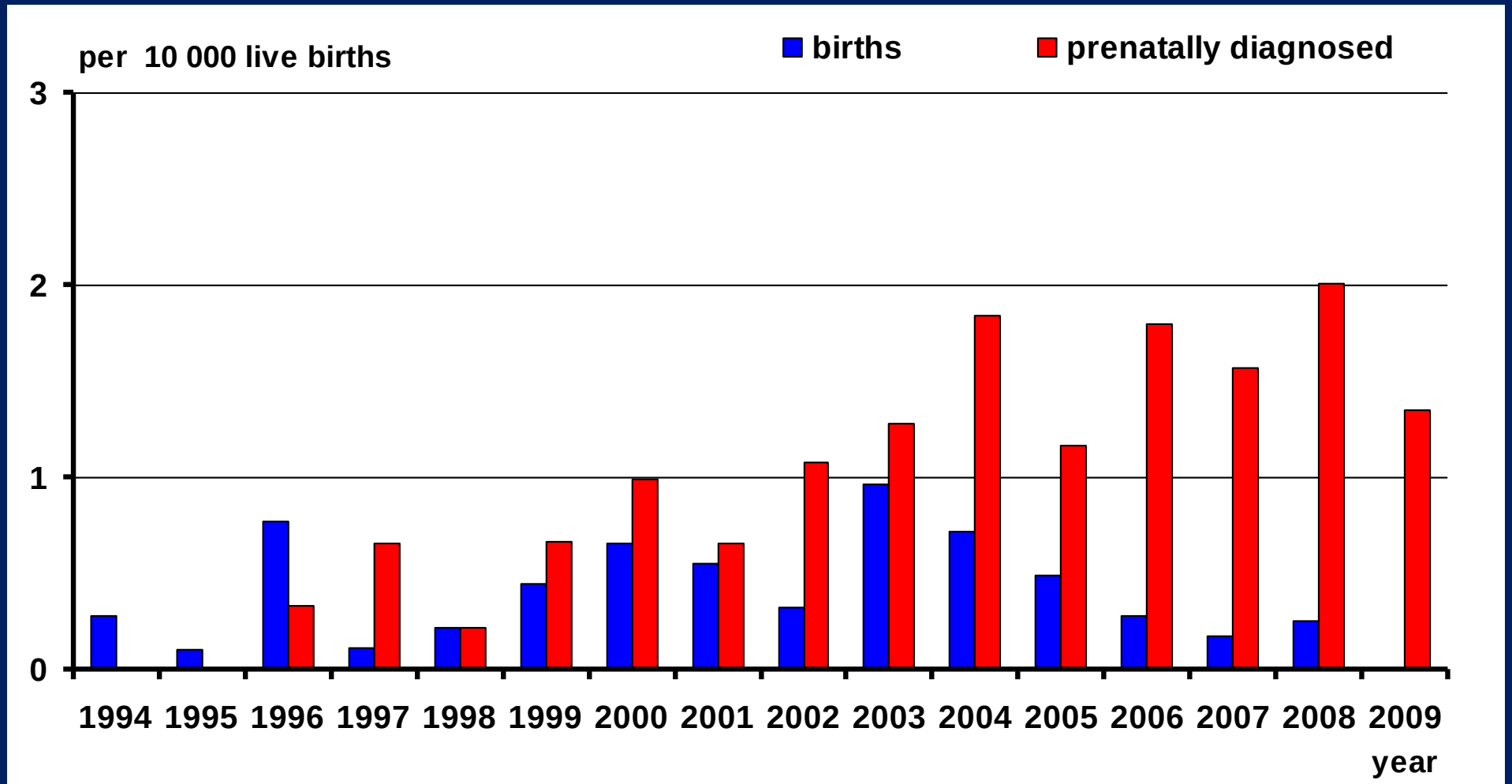
Incidence XXVII

Edwards Syndrome in Czech Rep. 1996 - 2009



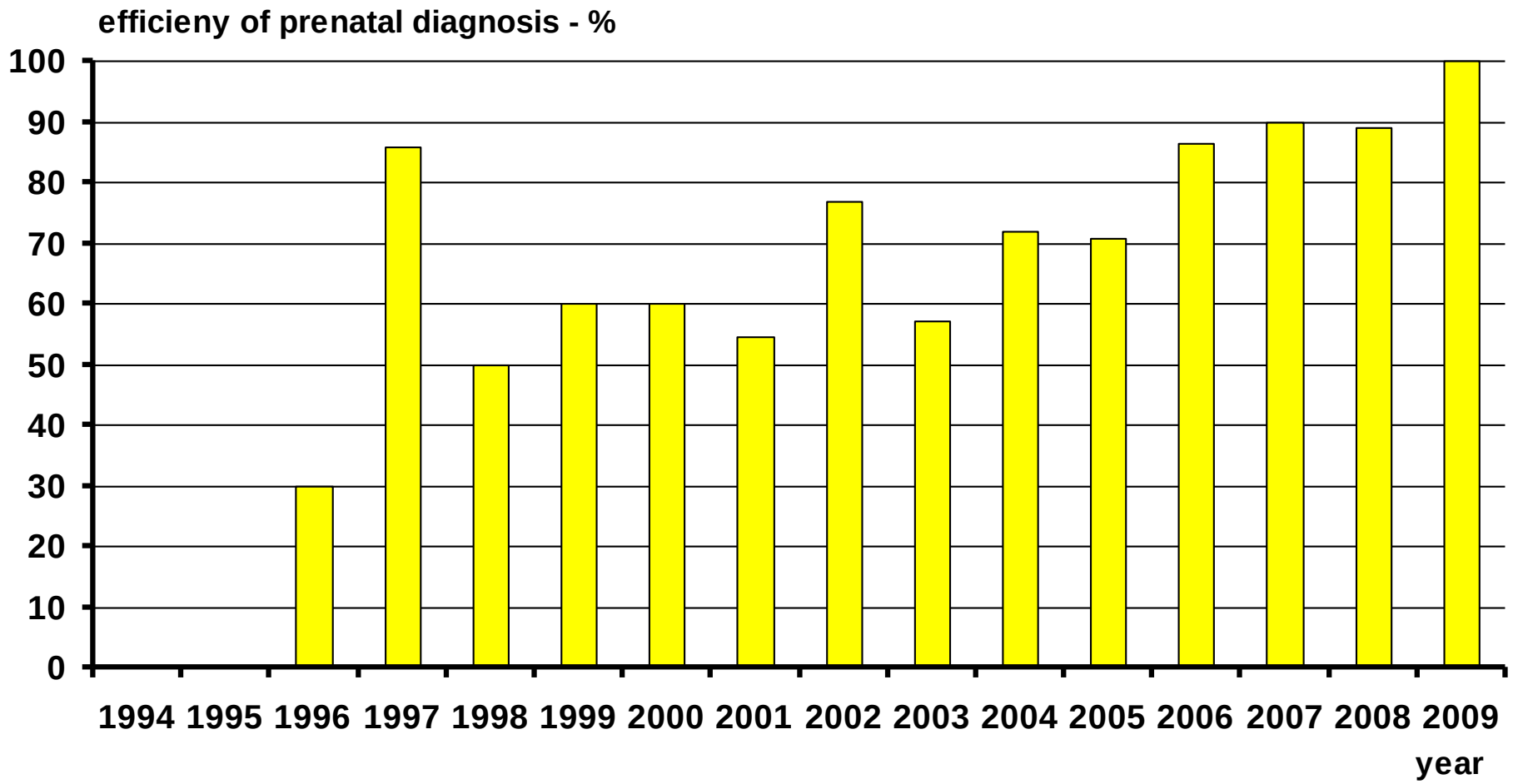
Incidence XXVIII

Patau Syndrome in Czech Rep. 1994 - 2009



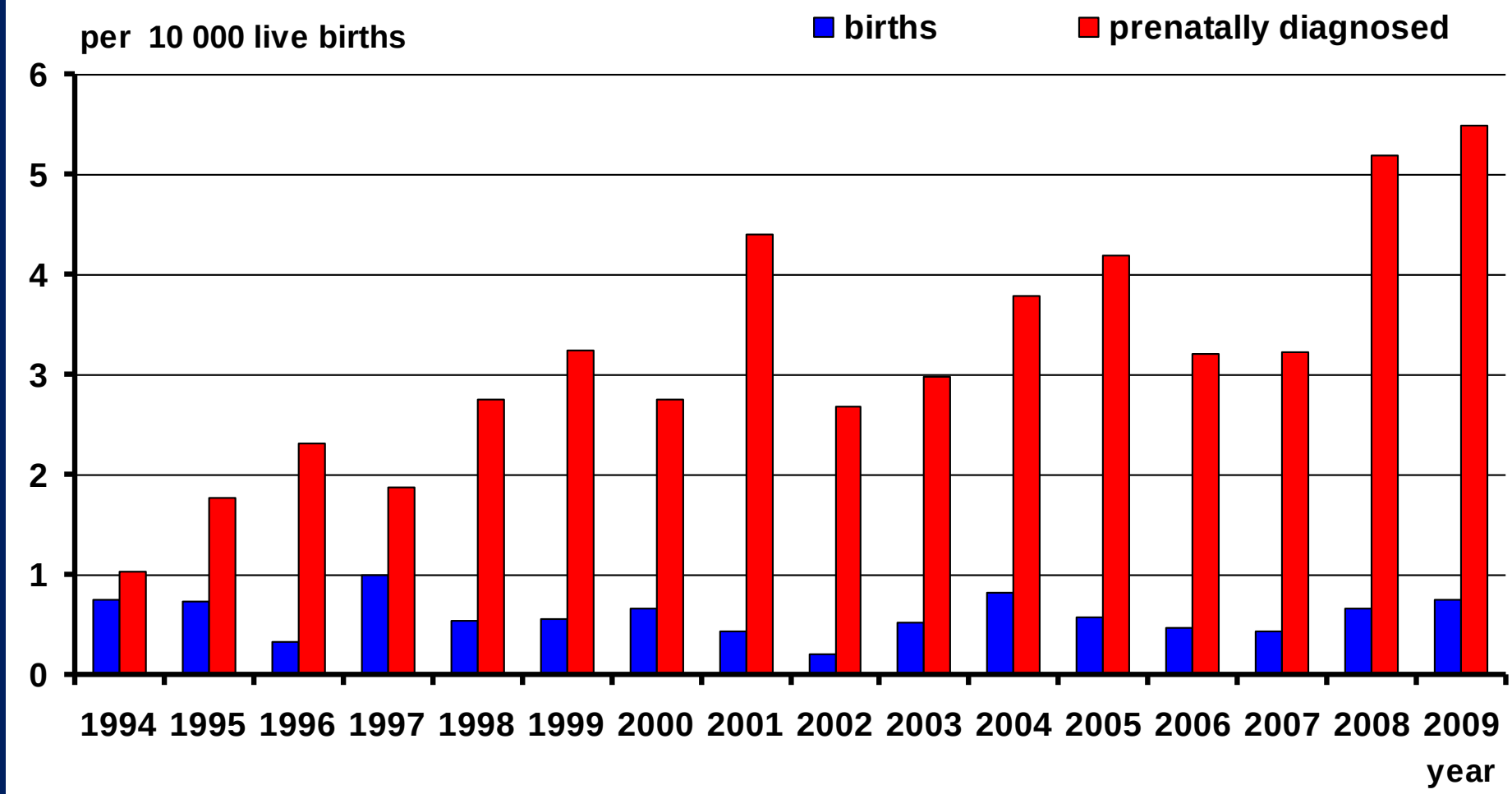
Incidence XXIX

Patau Syndrome in Czech Rep. 1996 - 2009



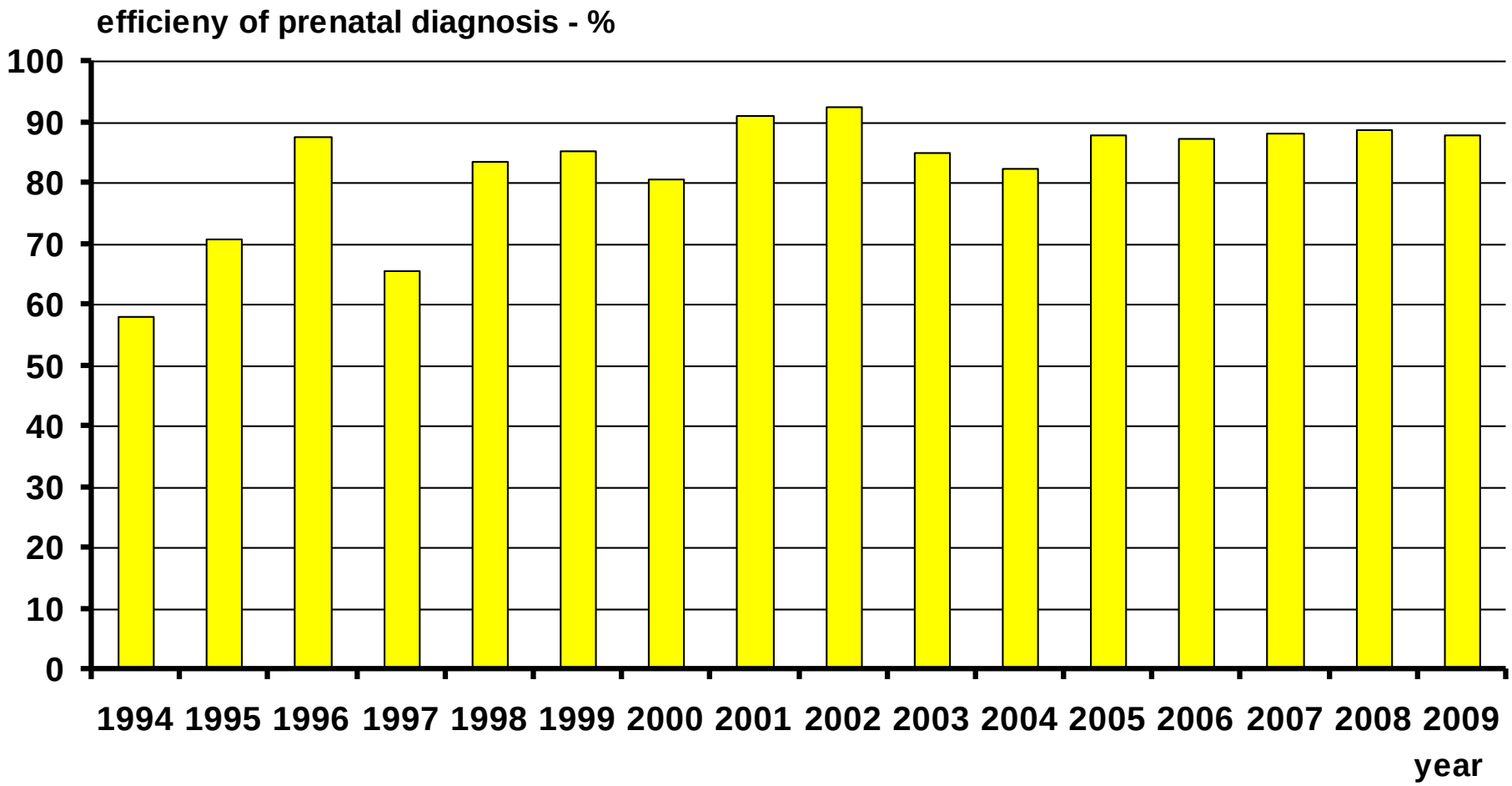
Incidence XXX

Turner Syndrome in Czech Rep. 1994 - 2009



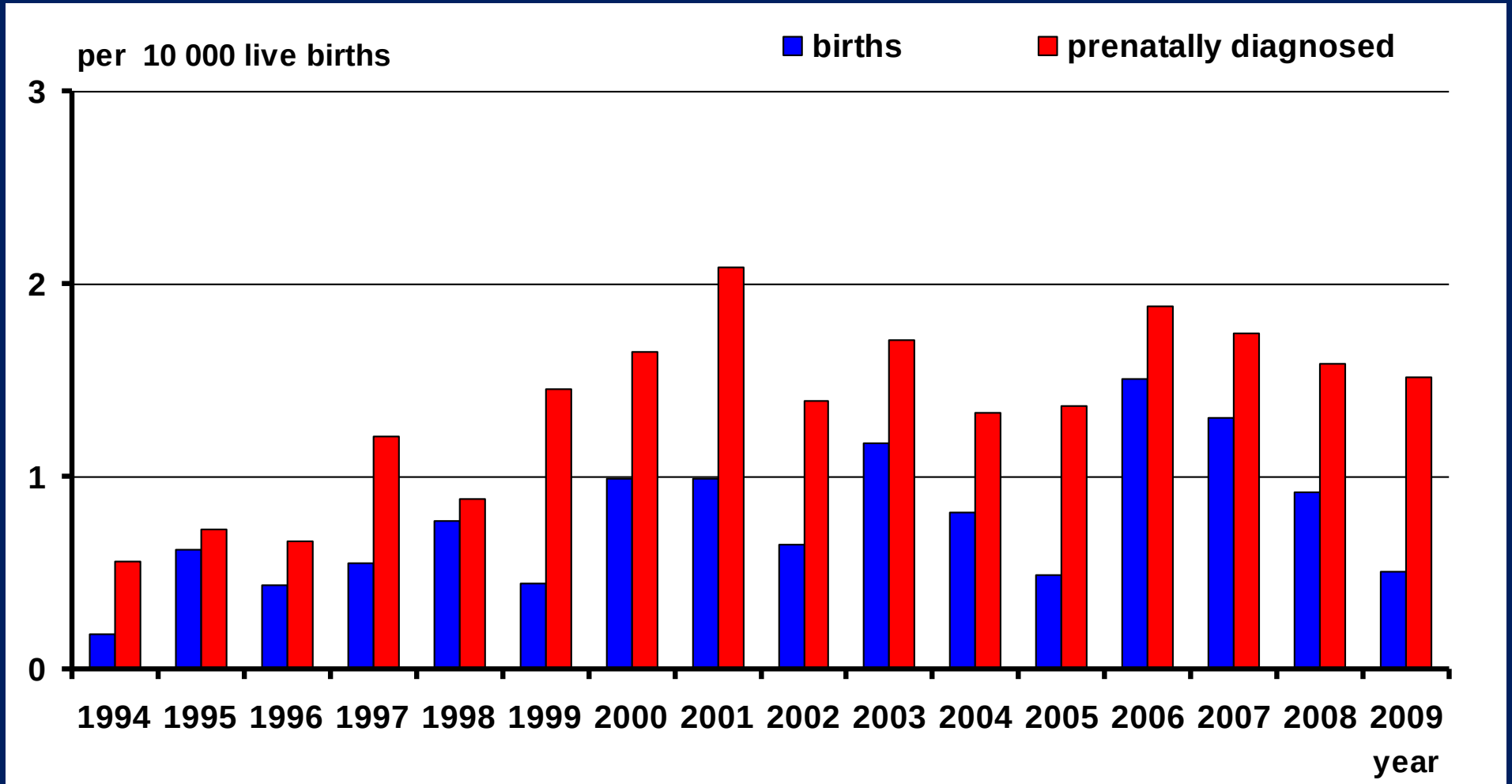
Incidence XXXI

Turner Syndrome in Czech Rep. 1996 - 2009



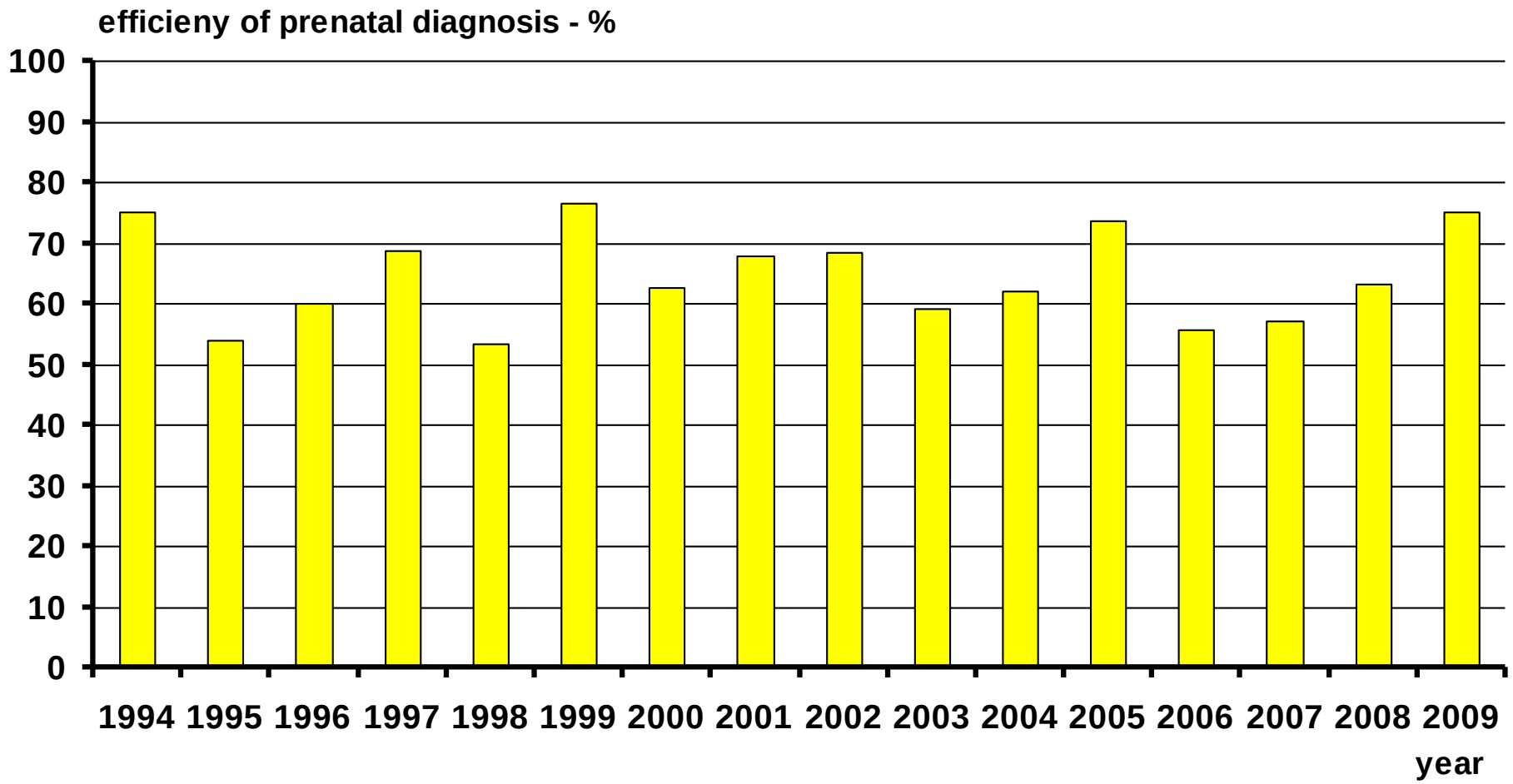
Incidence XXXII

Klinefelter Syndrome in Czech Rep. 1996 - 2009



Incidence XXXIII

Klinefelter Syndrome in Czech Rep. 1996 - 2009



Mortality and Morbidity

The role of congenital anomalies

Congenital anomalies are important causes of perinatal mortality and morbidity.

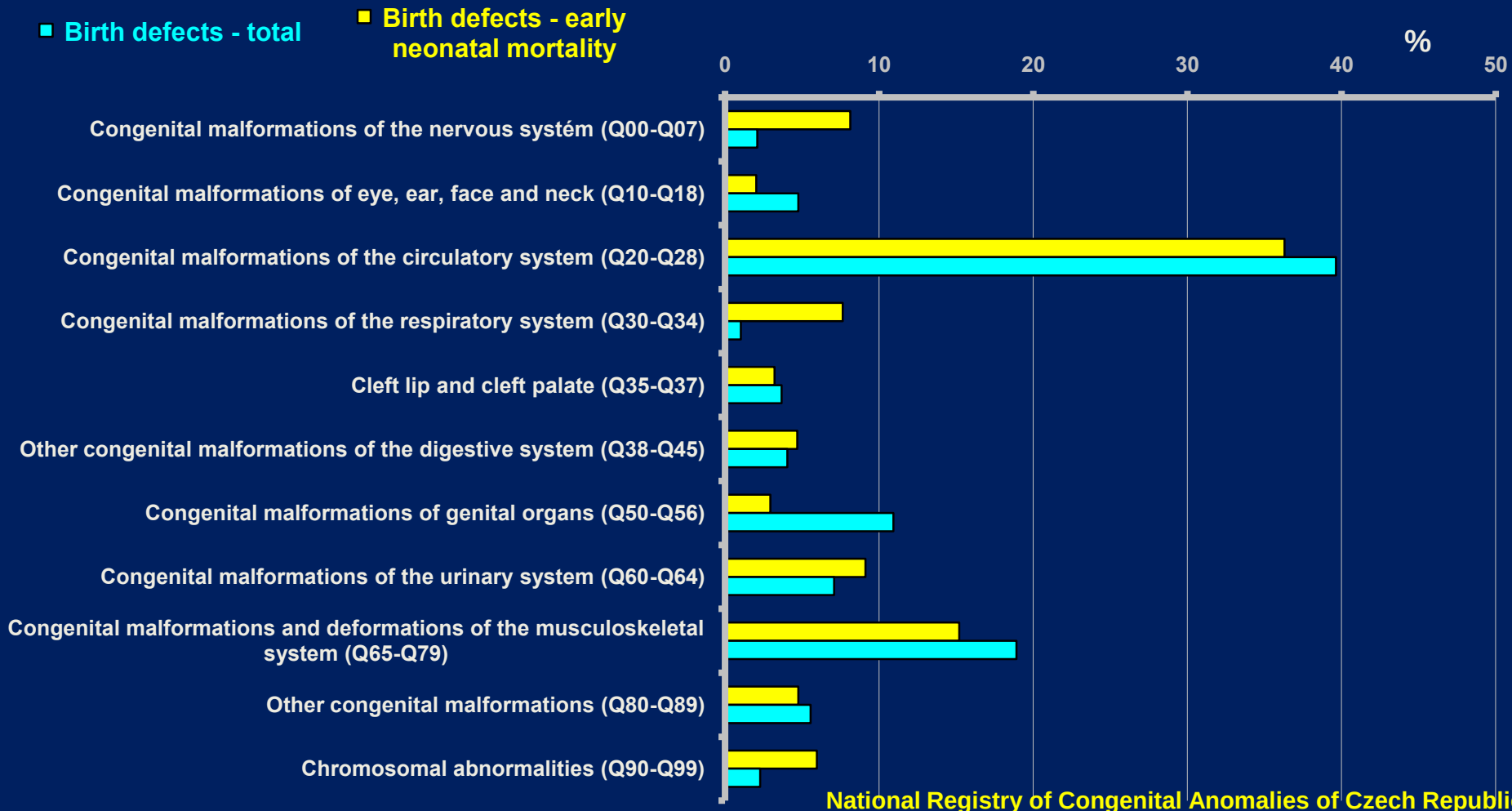
Perinatal mortality covers both Stillbirths and Early neonatal mortality.

The role of congenital anomalies in Stillbirths and in Early neonatal mortality is commonly analyzed.

We provide the results from our Registry.

Early neonatal mortality

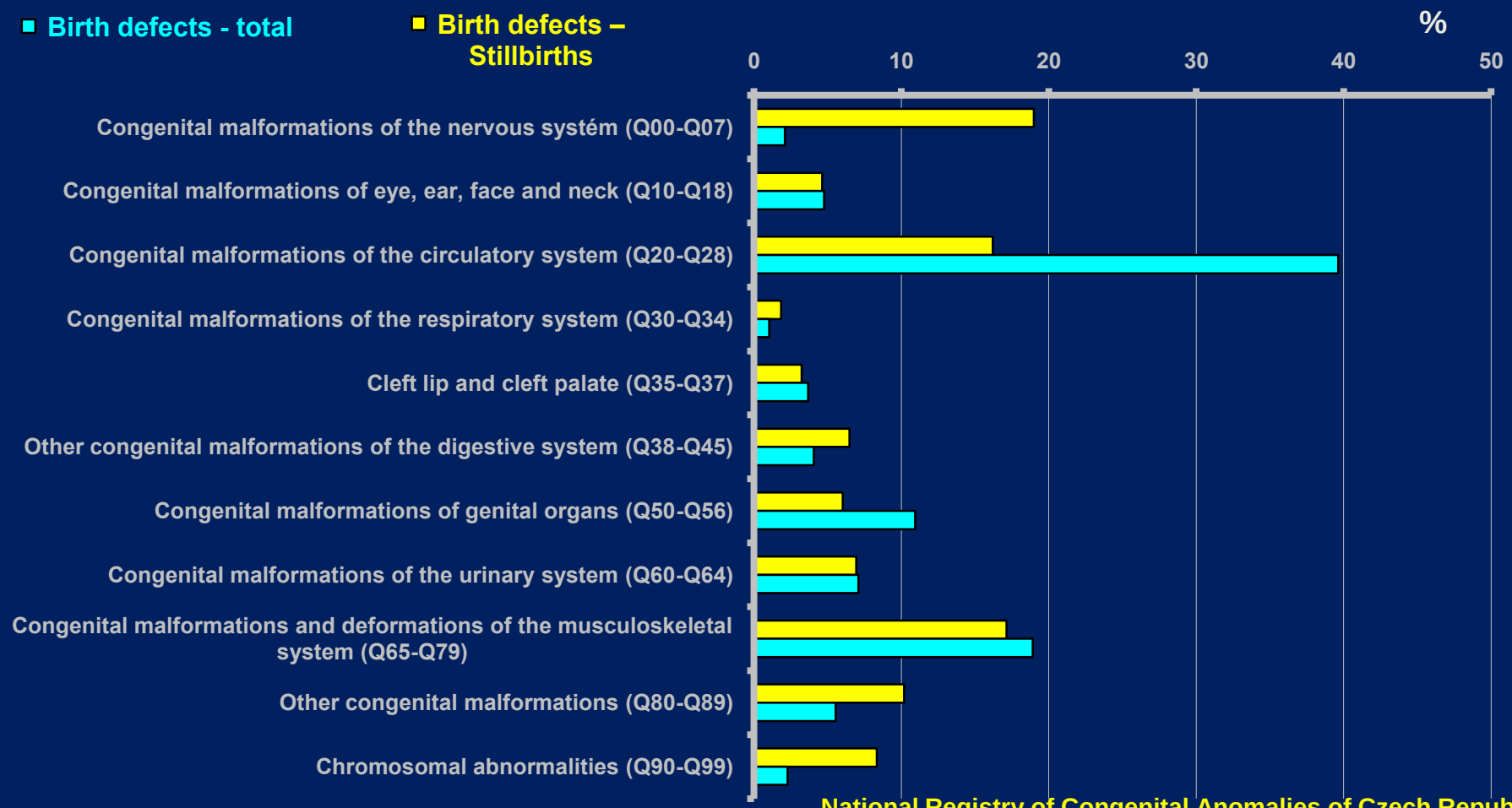
Birth defects and Early neonatal mortality



National Registry of Congenital Anomalies of Czech Republic

Stillbirths

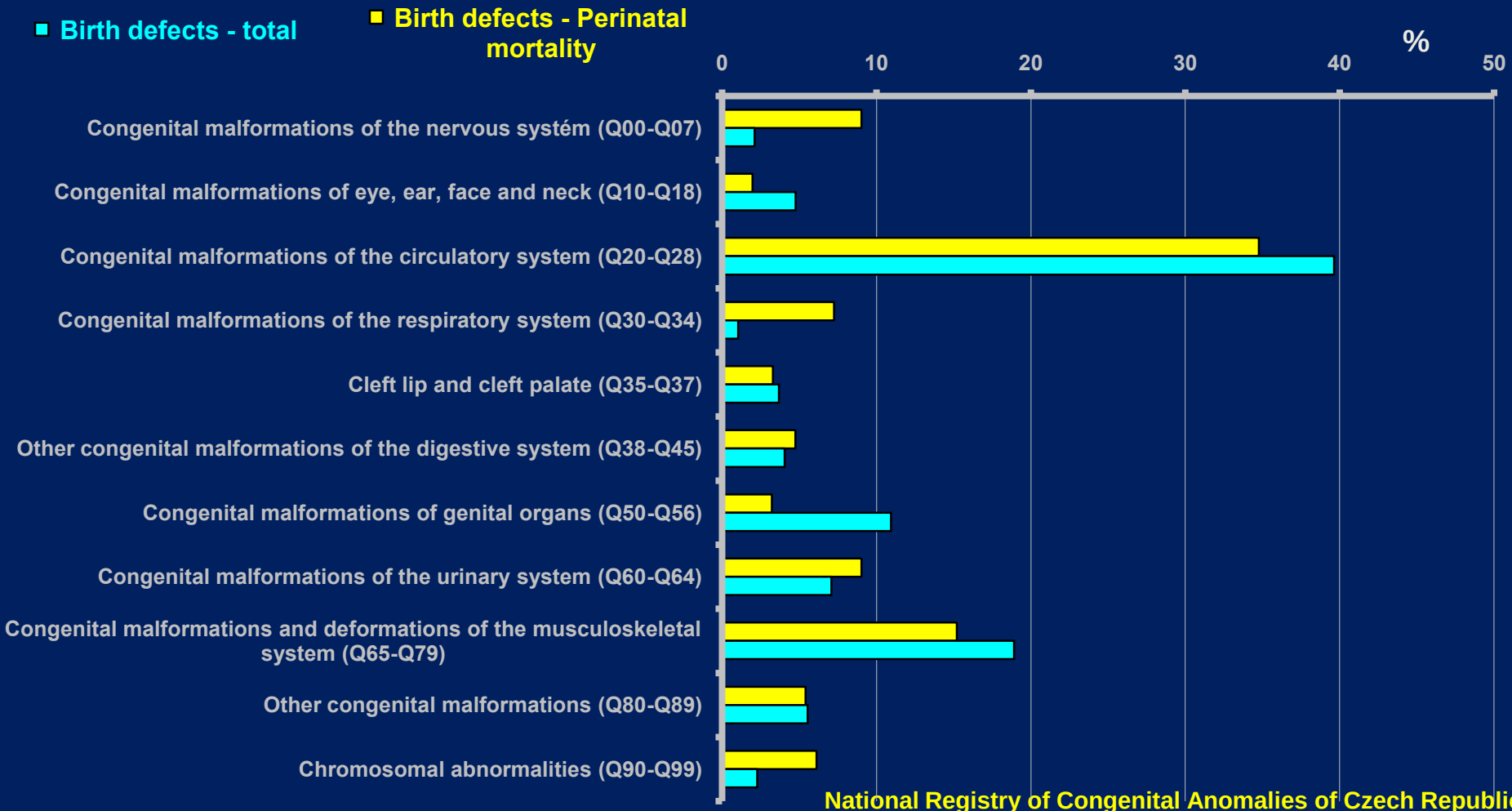
Birth defects and Stillbirths



National Registry of Congenital Anomalies of Czech Republic

Perinatal mortality

Birth defects and Perinatal mortality



National Registry of Congenital Anomalies of Czech Republic

Useful links

Registries and organizations

National Registry of Congenital Anomalies of the Czech Republic

http://www.uzis.cz/ **http://www.vrozene-vady.cz/**

International Clearinghouse for Birth Defects Surveillance and Research

http://www.icbdsr.org/

European Surveillance of Congenital Anomalies

http://www.eurocat.ulster.ac.uk/

Congenital anomalies

1. Definitions
2. Etiology, teratogens
3. Selected congenital anomalies
4. Prenatal diagnosis
5. Incidence of selected congenital anomalies
6. Summary

Summary I

Congenital anomalies can be caused by genetic, environmental or both factors.

The effects of teratogens is species-dependent, dose-dependent and time-dependent.
Be very careful with medicament therapy during pregnancy.

Prenatal diagnosis is complex and interdisciplinary domain, that requires the cooperation of medical geneticist, gynecologist, obstetrician, ultrasound diagnostician, clinical biochemist and (sometimes) other experts.

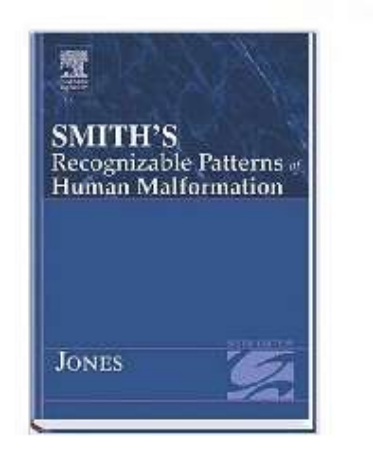
Summary II

The absolute and relative number of congenital anomalies in the Czech Republic is increasing. We believe, it is caused:
1) by the improvement of the prenatal diagnosis (especially by the combined screening of 1st trimester implementation), which is able to diagnose selected anomalies during the pregnancy earlier (some of those cases would formerly end as spontaneous abortions without diagnose)
2) by the increase of mean age of delivering women (what is a common trend today).

Congenital anomalies are important causes of perinatal mortality and morbidity. Prenatal diagnosis may bring useful information before delivery, so there is time to ensure essential perinatologic therapy.

Recommended literature

For those, who are further interested…



Jones, K.L.
Smith's Recognizable Patterns Of Human Malformation
Sixth edition

Saunders; 6th edition (August 17, 2005)

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This presentation (and other materials) can be downloaded from our website.

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Thank you

Thank you for your attention.